PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

United States Patent and Trademark Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 27 May 1999 (27.05.99)	
International application No. PCT/HU98/00076	**Applicant's or agent's file reference** 13256 KB
International filing date (day/month/year) 07 August 1998 (07.08.98)	**Priority date** (day/month/year) 12 August 1997 (12.08.97)
Applicant BARKÓCZY, József et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

02 March 1999 (02.03.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

C. Carrié

Telephone No.: (41-22) 338.83.38

PCT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
13256 KB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/HU 98/ 00076	07/08/1998	12/08/1997
Applicant		
EGIS GY GYSZERGY R RT. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. [ ] **Certain claims were found unsearchable** (see Box I).

2. [ ] **Unity of invention is lacking** (see Box II).

3. [ ] The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
   - [ ] filed with the international application.
   - [ ] furnished by the applicant separately from the international application,
     - [ ] but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
   - [ ] Transcribed by this Authority

4. With regard to the **title,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established by this Authority to read as follows:

1,3-Dioxolo/4,5-H//2,3/Benzodiazepine derivatives as Ampa/Kainate Receptor inhibitors

5. With regard to the **abstract,**
   - [ ] the text is approved as submitted by the applicant
   - [X] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is:

Figure No. _____
- [ ] as suggested by the applicant.
- [ ] because the applicant failed to suggest a figure.
- [ ] because this figure better characterizes the invention.

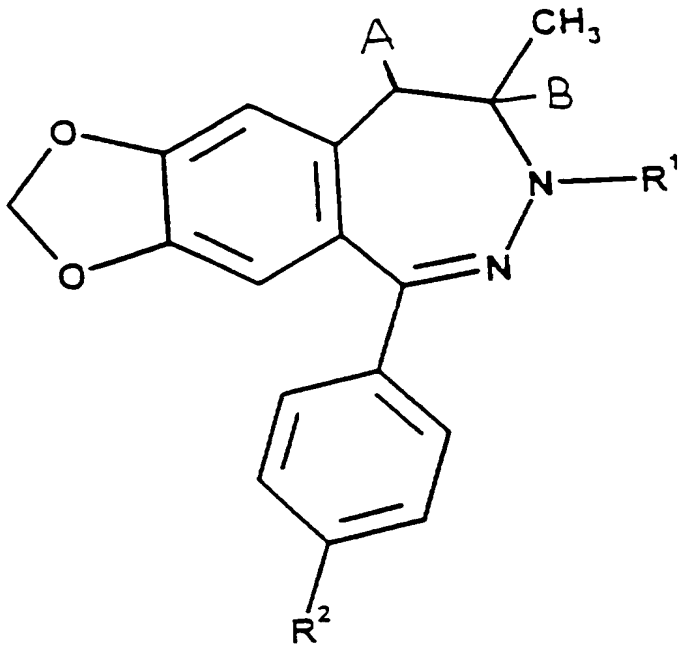
[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 98/00076

Box III TEXT OF THE ABSTRACT (Continuation of it m 5 of the first sheet)

The invention refers to 1,3-dioxollo-/4,5-h//2,3/benzodiazepine derivatives of the formula I



I

a process for preparing these compounds and to pharmaceutical compositions containing these active substances, which are used to selectively inhibit Ampa/Kainate receptors

INTERNATIONAL SEARCH REPORT

Inter[redacted] Application No
PCT/HU 98/00076

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/04 A61K31/55

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 699 678 A (LILLY CO ELI) 6 March 1996 see claim 1 ---	1-14
X	EP 0 699 677 A (LILLY CO ELI) 6 March 1996 see claim 1; examples 8,9,13-15,20 ---	1-14
X	WO 96 04283 A (SCHERING AG ;HAMORI TAMAS (HU); TARNAWA ISTVAN (HU); SOLYOM SANDOR) 15 February 1996 see claim 1; examples 46,47 ---	1-14
X	WO 95 01357 A (GYOGYSZERKUTATO INTEZET ;LING ISTVAN (HU); HAMORI TAMAS (HU); BOTK) 12 January 1995 see claim 1 ---	1-14
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 October 1998	19/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 98/00076

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 11262 A (GYOGYSZERKUTATO INTEZET) 9 July 1992 cited in the application see claims 1,4; examples 1,2,5,7,8	1-14
X	EP 0 492 485 A (GYOGYSZERKUTATO INTEZET) 1 July 1992 see claim 1; examples 2,8-10,15,16	1-14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 98/00076

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0699678 A	06-03-1996	AU 3035595 A	14-03-1996
		AU 696243 B	03-09-1998
		AU 3035695 A	14-03-1996
		AU 695424 B	13-08-1998
		AU 3035795 A	14-03-1996
		AU 689639 B	02-04-1998
		AU 3418695 A	22-03-1996
		BR 9503843 A	10-09-1996
		BR 9503844 A	10-09-1996
		BR 9503845 A	16-04-1996
		CA 2198751 A	07-03-1996
		CN 1122338 A	15-05-1996
		CN 1128264 A	07-08-1996
		CN 1123282 A	29-05-1996
		CZ 9502219 A	13-03-1996
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		FI 954064 A	01-03-1996
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		FI 970833 A	27-02-1997
		HU 72644 A	28-05-1996
		HU 72673 A	28-05-1996
		HU 72675 A	28-05-1996
		JP 8081468 A	26-03-1996
		JP 8092255 A	09-04-1996
		JP 8081469 A	26-03-1996
		JP 10505066 T	19-05-1998
		NO 953394 A	01-03-1996
		NO 953395 A	01-03-1996
		NO 953396 A	01-03-1996
		NZ 272896 A	24-03-1997
		NZ 272897 A	24-03-1997
		NZ 272898 A	20-12-1996
		PL 310226 A	04-03-1996
		PL 310228 A	04-03-1996
		WO 9606606 A	07-03-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 98/00076

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0699678 A		US 5665878 A	09-09-1997
		US 5795886 A	18-08-1998
EP 0699677 A	06-03-1996	US 5665878 A	09-09-1997
		AU 3035595 A	14-03-1996
		AU 696243 B	03-09-1998
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		AU 3035795 A	14-03-1996
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		AU 3418695 A	22-03-1996
		BR 9503843 A	10-09-1996
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		BR 9503845 A	16-04-1996
		CA 2198751 A	07-03-1996
		CN 1122338 A	15-05-1996
		CN 1128264 A	07-08-1996
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		CZ 9502219 A	13-03-1996
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		EP 0699676 A	06-03-1996
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		FI 954065 A	01-03-1996
		FI 954066 A	01-03-1996
		FI 970833 A	27-02-1997
		HU 72644 A	28-05-1996
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		HU 72675 A	28-05-1996
		JP 8081468 A	26-03-1996
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		NZ 272896 A	24-03-1997
		NZ 272897 A	24-03-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 98/00076

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		PL 310226 A	04-03-1996
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		WO 9606606 A	07-03-1996
		US 5795886 A	18-08-1998
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		AU 693241 B	25-06-1998
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		FI 970434 A	31-01-1997
		HU 76801 A	28-11-1997
		JP 10504543 T	06-05-1998
		NO 970435 A	31-01-1997
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		AU 7236394 A	24-01-1995
WO 9211262 A	09-07-1992	AU 9122691 A	22-07-1992
		CA 2098291 A	22-06-1992
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		JP 6506442 T	21-07-1994
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		CA 2057504 A	22-06-1992
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		CZ 9103985 A	19-01-1994
		DE 69128236 D	02-01-1998
		DE 69128236 T	14-05-1998
		ES 2112848 T	16-04-1998
		FI 916032 A	22-06-1992
		IL 100449 A	31-12-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 98/00076

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0492485 A		JP 2756742 B	25-05-1998
		JP 5070463 A	23-03-1993
		MX 9102734 A	01-06-1992
		NO 300376 B	20-05-1997
		NZ 241110 A	27-04-1994
		SI 9111966 A	30-04-1998
		US 5604223 A	18-02-1997
		US 5536832 A	16-07-1996
		US 5519019 A	21-05-1996
		US 5521174 A	28-05-1996
		US 5639751 A	17-06-1997

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 13256 KB

Box No. I TITLE OF INVENTION Novel 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives, a pharmaceutical composition containing the same, and a process for the preparation of the active ingredient

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

EGIS GYÓGYSZERGYÁR RT.
Budapest, Keresztúri út 30-38. H-1106
Hungary

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (i.e. country) of residence if no State of residence is indicated below.)*

BARKÓCZY, József
Budapest, Szirom u. 4-6/b. H-1016,
Hungary

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ADVOPATENT Office of Patent and Trademark Attorneys
Budapest, P.O.Box 11, H-1251
Hungary

Telephone No. (36-1) 201-1528

Facsimile No. (36-1) 201-1692

Teleprinter No.

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

CSELENYÁK, Judit
Budapest, Tomán István u. 4. H-1124
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RÁTKAI, Zoltán
Budapest, Morvai u. 19. H-1101
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SIMIG, Gyula
Budapest, Hollósy Simon u. 25. H-1126
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BALÁZS, László
Budapest, Baross u. 38. H-1088
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DOMÁN, Imre
Budapest, Mohács u. 18/B, H-1135
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KÓTAY NAGY, Péter
Vác, Nagymező u. 73. H-2600
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GREFF, Zoltán
Budapest, Gyöngyvirág u. 8. H-1028
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SERES, Péter
Budapest, Rädda Barnen u. 6. H-1153
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SZABÓ, Géza
Budapest, Hold u. 25., H-1054
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GACSÁLYI, István
Budapest, Tárogató u. 64/b. H-1021
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GIGLER, Gábor
Budapest, Teréz krt. 41. H-1067
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GYERTYÁN, István
Budapest, Koronafürt u. 33. H-1165
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
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[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

LÉVAY, György
Budakeszi, Fő tér 3. H-2092
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KOVÁCS, Attila
Dorog, Goethe u. 15. H-2510
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SIMÓ, Annamária
Budapest, Radnóti M. u. 24. H-1137
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

SZABADOS, Tamás
Budapest, Dombtető u. 2. H-1108
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This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

[X] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Continuation of Box No. III FURTHER APPLICANTS AND/OR (FURTHER) INVENTORS

If none of the following sub-boxes is used, this sheet is not to be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

EGYED, András
Budapest, Újvidék u. 58. H-1145
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This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

VÉGH, Miklós
Budapest, Szondy u. 89. H-1068
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

TIHANYI, Károly
Budapest, Postamester u. 37. H-1171
Hungary

This person is:
- [ ] applicant only
- [X] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality: Hungary

State *(i.e. country)* of residence: Hungary

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [X] the United States of America only
- [ ] the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

This person is:
- [ ] applicant only
- [ ] applicant and inventor
- [ ] inventor only *(If this check-box is marked, do not fill in below.)*

State *(i.e. country)* of nationality:

State *(i.e. country)* of residence:

This person is applicant for the purposes of:
- [ ] all designated States
- [ ] all designated States except the United States of America
- [ ] the United States of America only
- [ ] the States indicated in the Supplemental Box

- [ ] Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes: at least one must be marked)*:

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

- ☒ AL Albania .....
- ☒ AM Armenia .....
- ☒ AT Austria .....
- ☒ AU Australia .....
- ☒ AZ Azerbaijan
- ☒ BA Bosnia and Herzegovina .....
- ☒ BB Barbados
- ☒ BG Bulgaria .....
- ☒ BR Brazil .....
- ☒ BY Belarus
- ☒ CA Canada
- ☒ CH and LI Switzerland and Liechtenstein
- ☒ CN China .....
- ☒ CU Cuba .....
- ☒ CZ Czech Republic .....
- ☒ DE Germany .....
- ☒ DK Denmark .....
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- ☒ ID Indonesia
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- ☒ KE Kenya .....
- ☒ KG Kyrgyzstan .....
- ☒ KP Democratic People's Republic of Korea .....
- ☒ KR Republic of Korea .....
- ☒ KZ Kazakhstan .....
- ☒ LC Saint Lucia
- ☒ LK Sri Lanka
- ☒ LR Liberia
- ☒ LS Lesotho .....
- ☒ LT Lithuania
- ☒ LU Luxembourg
- ☒ LV Latvia
- ☒ MD Republic of Moldova .....
- ☒ MG Madagascar .....
- ☒ MK The former Yugoslav Republic of Macedonia .....
- ☒ MN Mongolia
- ☒ MW Malawi .....
- ☒ MX Mexico .....
- ☒ NO Norway
- ☒ NZ New Zealand .....
- ☒ PL Poland .....
- ☒ PT Portugal .....
- ☒ RO Romania
- ☒ RU Russian Federation .....
- ☒ SD Sudan
- ☒ SE Sweden
- ☒ SG Singapore
- ☒ SI Slovenia .....
- ☒ SK Slovakia .....
- ☒ SL Sierra Leone
- ☒ TJ Tajikistan .....
- ☒ TM Turkmenistan .....
- ☒ TR Turkey .....
- ☒ TT Trinidad and Tobago .....
- ☒ UA Ukraine .....
- ☒ UG Uganda .....
- ☒ US United States of America .....
- ☒ UZ Uzbekistan .....
- ☒ VN Viet Nam .....
- ☒ YU Yugoslavia .....
- ☒ ZW Zimbabwe .....

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....
- ☐ .....

In addition to the designations made above, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except the designation(s) of _____

The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM Further priority claims are indicated in the Supplemental Box ☐

The priority of the following earlier application(s) is hereby claimed:

Country *(in which, or for which, the application was filed)*	Filing Date *(day/month/year)*	Application No.	Office of filing *(only for regional or international application)*
item (1) Hungary	12/August/1997 (12.08.97)	P 97 01382	
item (2) Hungary	12/August/1997 (12.08.97)	P 97 01383	
item (3)			

Mark the following check-box if the certified copy of the earlier application is to be issued by the Office which for the purposes of the present international application is the receiving Office (a fee may be required):

[X] The receiving Office is hereby requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s): _____

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):* ISA / EP

Earlier search *Fill in where a search (international, international-type or other) by the International Searching Authority has already been carried out or requested and the Authority is now requested to base the international search, to the extent possible, on the results of that earlier search. Identify such search or request either by reference to the relevant application (or the translation thereof) or by reference to the search request:*

Country (or regional Office): Date *(day/month/year)*: Number:

Box No. VIII CHECK LIST

This international application contains the following number of sheets:

1. request	8	sheets
2. description	101	sheets
3. claims	30	sheets
4. abstract	1	sheets
5. drawings		sheets
Total	140	sheets

This international application is accompanied by the item(s) marked below:

1. [X] separate signed power of attorney
2. [ ] copy of general power of attorney
3. [ ] statement explaining lack of signature
4. [ ] priority document(s) *identified in Box No. VI as item(s):*
5. [X] fee calculation sheet
6. [ ] separate indications concerning deposited microorganisms
7. [ ] nucleotide and/or amino acid sequence listing (diskette)
8. [ ] other *(specify)*:

Figure No. _____ of the drawings (if any) should accompany the abstract when it is published.

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

KARÁCSONYI, Béla
Patent Attorney

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: [ ] received: [ ] not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority specified by the applicant: ISA /
6. [ ] Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 13256 KB

Applicant: EGIS GYÓGYSZERGYÁR RT., Budapest, Keresztúri út 30-38. H-1106 Hungary

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . HUF . . . 13500.- T
2. SEARCH FEE . . . . . DEM . . . 2200.- S

International search to be carried out by EP

(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

The international application contains 140 sheets.

first 30 sheets . . . . . CHF . . . 650.- b_1

110 (remaining sheets) x 15 (additional amount) = 1650.- b_2

Add amounts entered at b_1 and b_2 and enter total at B . . . CHF 2300.- B

Designation Fees

The international application contains _____ designations.

11 (number of designation fees payable *(maximum 11)*) x 150 CHF (amount of designation fee) = 1650.- D

Add amounts entered at B and D and enter total at I . . . . . CHF . . . 3950.- I

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT . . . . . P
5. TOTAL FEES PAYABLE

Add amounts entered at T, S, I and P, and enter total in the TOTAL box . . TOTAL

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

- ☐ authorization to charge deposit account (see below)
- ☐ cheque
- ☐ postal money order
- ☒ bank draft
- ☐ cash
- ☐ revenue stamps
- ☐ coupons
- ☐ other *(specify):*

DEPOSIT ACCOUNT AUTHORIZATION *(this mode of payment may not be available at all receiving Offices)*

The RO/ _____

- ☐ is hereby authorized to charge the total fees indicated above to my deposit account.
- ☐ is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.
- ☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

Deposit Account Number _____ Date *(day/month/year)* _____ Signature _____

See Notes to the fee calculation sheet

18

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
13256 KB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU98/00076	07/08/1998	12/08/1997
International Patent Classification (IPC) or national classification and IPC C07D491/04		
Applicant EGIS GY GYSZERGY R RT. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02/03/1999	09. 11. 99
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Gettins, M Telephone No. +49 89 2399 8273

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU98/00076

I. Basis f the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-101 as originally filed

Claims, No.:

1-17 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they hav been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 16.

because:

☒ the said international application, or the said claims Nos. 16 relate to th following subject matter which does not require an international preliminary examination (*specify*):

s e s parate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-15,17
	No:	Claims	

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate she t

1). Relevant prior art is provided by:
(A) WO96/04283
(B) WO95/01357
(C) EP699678
(D) EP492485
(E) WO92/12262
(F) EP699677

2). The current application is novel vis-à-vis (B), (C) and (E) on account of the R^1 group.

There is an overlap between the current application and the compounds of (F) wherein X is acyl whereby acyl (page 4, line 50) can be carbamoyl or N-methylcarbamoyl. There is an overlap between the compounds of (D) wherein R is an acyl group substituted by amino or by (di)alkylamino and the current application. Although in both cases no specific novelty destroying compounds are exemplified the overlapping range is considered to be novelty destroying. The current application overlaps with the disclosure of (A) wherein R^3 is an optionally substituted alkyl or an alkoxy group. Examples 46 and 47 of (A) appear to specifically anticipate the compounds of the current application in which R^1 is $-CO-(CH_2)_p-R^6$ where p is zero and R^6 is alkoxy. While the overlap with R^{10} of (A) as substituted alkyl can be seen as a novel selection the overlapping range with R^{10} of (A) as alkoxy is novelty destroying and should be removed.

3). The compounds of the current application are benzodiazepine derivatives which act as selective inhibitors of AMPA receptors. Benzodiazepine derivatives are known from (A)-(F) to have an effect upon the CNS and from (A)-(C) and (F) it is specifically known that they can act as AMPA receptor inhibitors. Given the very close prior art the problem outlined by the Applicant on page 6 must be considered to be the problem underlying the current application i.e. the provision of further benzodiazepine derivatives which are more effective (as AMPA inhibitors) than the closest prior art. The Applicant has submitted comparative test data in which test compound "A" is compared with compounds of the current application. The comparative test compound "A" is not however considered to be

the closest prior art. This appears to be provided by (A), examples 46 and 47. Since no tests have been carried out against the closest prior art the problem cannot be considered to have been shown to have been solved and an inventive step cannot be acknowledged.

The Applicant is asked to demonstrate that the problem underlying the current application has in fact been solved. In order to be fully convincing any comparative tests used to demonstrate this must be carried out against the structurally closest prior art. It is however pointed out that an inventive step would have to be made credible for the full scope of the current application. In particular the Applicant should ensure that it is credible that the full scope of R^1 and of R^2 (i.e. not just amino, but also (di)alkylamino or acylamino) solve the given problem. Specific compounds are for instance exemplified in the prior art where R^2 is nitro (see e.g. (A), (B) or (C)) or acylamino (see e.g. (B), (C)) and compounds are exemplified where R^3 is a variety of substituents : hydrogen (see (B) and (C)); .

In order to be fully convincing the Applicant would need to show that differences at these positions lead, when compared with the closest prior art, to an unexpected quantitative improvement in activity.

4). Claims 16 and 17 should be made more concise and readily comprehensible by means of a reference back to claim 1 (Article 6 PCT). The definitions thereby rendered redundant should be deleted. Similarly claims 9-15 should refer back to claims 1-7 respectively.

5). Claim 16 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject matter of this claim (Article 34(4)(a)(i)PCT).

6.) The current application describes compounds which have a single or double bond between the 8 and 9 positions. Numerous examples however refer to 7,8-dihydro. The Applicant should clarify whether or not these references should in fact be 8,9-dihydro?

7). The Applicant should cite and briefly discuss the prior art documents (A)-(D) and (F) (Rule 5.1 (a) (ii) PCT).

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 491/04, A61K 31/55 | A1

(11) International Publication Number: **WO 99/07708**

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(30) Priority Data:

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P 97 01383	12 August 1997 (12.08.97)	HU

(71) Applicant *(for all designated States except US)*: EGIS GYÓGYSZERGYÁR RT. [HU/HU]; Keresztúri út 30–38, H–1106 Budapest (HU).

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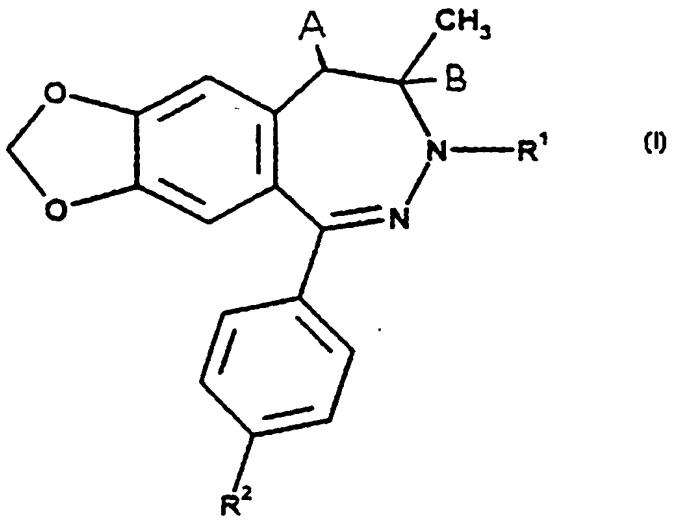
(74) Agent: ADVOPATENT OFFICE OF PATENT AND TRADEMARK ATTORNEYS; P.O. Box 11, H–1251 Budapest (HU).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: 1,3–DIOXOLO/4,5–H//2,3/BENZODIAZEPINE DERIVATIVES AS AMPA/KAINATE RECEPTOR INHIBITOR



(I)

(57) Abstract

The invention refers to 1,3–dioxolo–/4,5–h//2,3/benzodiazepine derivatives of formula (I), a process for preparing these compounds and to pharmaceutical compositions containing these active substances, which are used to selectively inhibit Ampa/Kainate receptors.

FOR THE PURPOSES OF INFORMATION ONLY

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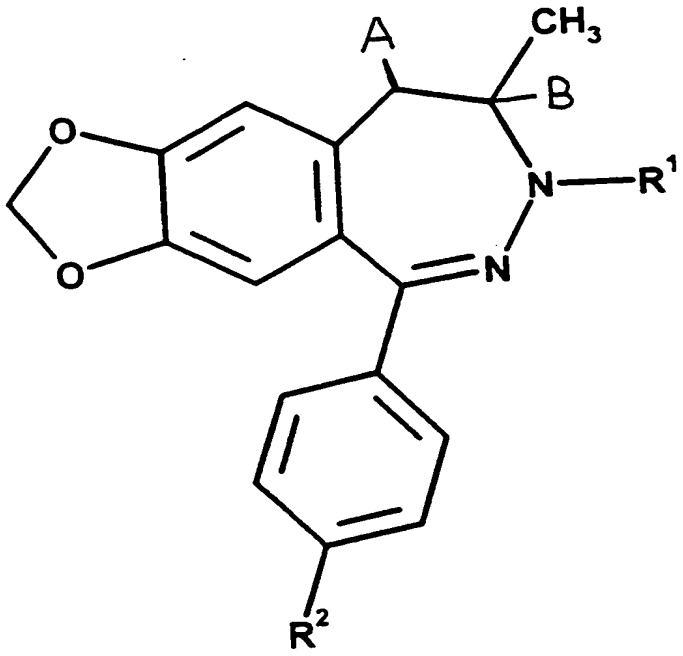
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

1,3-DIOXOLO/4,5-H//2,3/BENZODIAZEPINE DERIVATIVES AS AMPA/KAINATE RECEPTOR INHIBITORS

Novel 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives, a pharmaceutical composition containing the same, and a process for the preparation of the active ingredient

The invention refers to novel 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives, a pharmaceutical composition containing the same, and a process for the preparation of the active ingredient.

More specifically, the invention refers to novel 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives of the formula I



I

wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a C_{3-6} cycloalkyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two C_{1-4} alkyl group(s), a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 substituent(s), wherein the substituent consists of a C_{1-4} alkoxy group, or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 substituents, wherein the

substituent is a C_{1-4} alkoxy group,

n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2, or

A forms together with B a valence bond between the carbon atoms in positions 8 and 9, and in this case

R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group, a C_{3-6} cycloalkyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C_{1-4} alkoxy group, or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a

nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 3 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a halo atom or a C_{1-4} alkoxy group, and, in case of the phenoxy(C_{1-4} alkyl) group, the alkyl group is optionally substituted by 1 or 2 hydroxy group(s),

p has a value of 0, 1 or 2,

R^2 stands for a nitro group, an amino group or a (C_{1-4} alkanoyl)amino group,

and pharmaceutically suitable acid addition salts thereof.

Several 2,3-benzodiazepine derivatives having biological activity are known.

Tofisopam i.e. 1-(3,4-dimethoxyphenyl)--5-ethyl-7,8-dimethoxy-4-methyl-5H-2,3--benzodiazepine having anxiolytic effect is known from HU-P No. 155 572 and GB-P No. 1 202 579, respectively. The known compound does not comprise the ring system 1,3-dioxolo-

/4,5-h//2,3/benzodiazepine.

From HU-P No. 186 760, 7,8-dihydro-8--methyl-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives having effect on the central nervous system are known, among others. The known compounds are prepared by reducing the corresponding 8-methyl-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine derivative.

Various substituted 8-methyl-9H-1,3--dioxolo/4,5-h//2,3/benzodiazepine derivatives are known from HU-P No. 191 698 and the corresponding GB-P No. 2 162 184. The known compounds have antiaggressive and anxiolytic activities.

A novel process for the preparation of partly new 8-methyl-9H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine derivatives having antiaggressive activity is known from HU-P No. 191 702. According to the novel process, the suitably substituted 2-acetonyl-4,5--methylenedioxybenzophenone is reacted with an excess of hydrazine hydrate.

Further 7,8-dihydro-8-methyl-9H-1,3--dioxolo/4,5-h//2,3/benzodiazepine derivatives having antidepressant and antiparkinsonian activities are known from HU-P No. 206 719.

Some of the 2,3-benzodiazepine derivatives elicit their effect through the non-competitive inhibition of the AMPA/kainate receptors /Donevan, S.D. et al., J. Pharmacol. Exp. Ther., 271, 25-29 (1994)/.

From the literature it is known that

AMPA/kainate receptors play an important role in the acute and chronic diseases of the central nervous system. Through the inhibition of these receptors, muscle relaxant, neuroprotective and anticonvulsive effects can be achieved /Vizi, E.S. et al., CNS Drug Reviews, 2, 91-126 (1996); Lees, G.L., CNS Drugs, 5, 51-74 (1996)/.

The aim of the invention is to prepare novel 2,3-benzodiazepine derivatives that are more effective and less toxic, respectively, than the known 2,3-benzodiazepine derivatives.

It was found that the above aim is achieved by the novel 1,3-dioxolo/4,5-h//2,3/-benzodiazepine derivatives which have - due to their non-competitive AMPA/kainate effect - considerable muscle relaxant, neuroprotective and anticonvulsive activities. Thus, the novel compounds can be employed for the treatment of any diseases (such as epilepsy, diseases resulting in muscle spasm, various neurodegenerative diseases. stroke,) in which the inhibition of the AMPA/kainate receptors is favourable.

In the description and Claims, in the definition of the substituents, under a halo atom primarily a fluoro, chloro, bromo or iodo atom, preferably a fluoro or a chloro atom is meant.

A C_{1-4} alkyl group is a methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.-butyl,

tert.-butyl or isobutyl group. Preferably, a C_{1-4} alkyl group is a methyl, an ethyl or an isopropyl group.

A C_{1-4} alkoxy group is, primarily, a methoxy, ethoxy, n-propoxy, isopropoxy or n-butoxy group, preferably a methoxy group.

A C_{1-4} alkanoyl group is, primarily, a formyl, acetyl or n-propionyl group. Preferably, a C_{1-4} alkanoyl group is an acetyl or a propionyl group.

A C_{3-6} cycloalkyl group is a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group, preferably a cyclopropyl group.

A saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom is preferably a pyrrolidinyl, piperidinyl, piperazinyl, imidazolyl, triazolyl or morpholino group.

Suitably, the other nitrogen atom of the piperazinyl group is substituted.

In the definition of R^3 and R^4, wherein, together with the adjacent nitrogen atom, they form a saturated or unsaturated heterocyclic group having 5 or 6 members, said group is a heterocyclic group that comprises one or two nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and the heterocyclic ring contains no double bond or it contains one or more double bond(s). The nitrogen atom or one of the nitrogen atoms of the heterocyclic group

is attached to the carbonyl group in the definition of R^1. Such a heterocyclic group is, for example, a pyrrolidinyl, piperidinyl, pyridyl, morpholino, piperazinyl etc. group. Preferably, the above heterocyclic group is a pirrolidinyl, pyridinyl, morpholino or piperazinyl group. Especially preferably, said heterocyclic group is a piperazinyl group. Suitably, the other nitrogen atom of the piperazinyl group is substituted.

Under a pharmaceutically suitable acid addition salt an acid addition salt formed with a pharmaceutically suitable inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid etc. or with a pharmaceutically suitable organic acid such as formic acid, acetic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, succinic acid, citric acid, methanesulfonic acid etc. is meant.

The invention includes any isomers of the compounds of the formula I and the mixtures thereof.

Under the isomers of the compounds of the formula I - due to the presence of at least one chiral centre - both enantiomers, and - because of isomerisms that exist in case of certain substitutions - the isomers E and Z, diastereomers, tautomeric forms, and the mixtures thereof such as the racemate are meant.

A preferred subgroup of the compounds

of the formula I consists of the 7,8-dihydro--8-methyl-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives and pharmaceutically suitable acid addition salts thereof, wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a chloro atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a cyclopropyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two methyl group(s) or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and the heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 methoxy groups,

or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group

that is optionally substituted by 1 to 3 methoxy groups, n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group.

Within the above subgroup, suitable 7,8--dihydro-8-methyl-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine derivatives are the following compounds of the formula I, wherein

R^3 and R^4 represent, independently, a hydrogen atom, a cyclopropyl group, a methoxy group, an amino group, a dimethylaminophenyl group or a C_{1-2} alkyl group which latter is substituted by a phenyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl group, or

R^3 and R^4 form, together with the adjacent nitrogen atom and optionally a further nitrogen atom or oxygen atom, an imidazolyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl group,

n has a value of 0 or 1,

m has a value of 0 or 1,

R^2 stands for a nitro group or an amino group,

A represents a hydrogen atom,

B means a hydrogen atom,

and pharmaceutically suitable acid addition salts thereof.

The especially preferred 7,8-dihydro--8-methyl-9H-1,3-dioxolo/4,5-h//2,3/benzo-

diazepine derivatives are the following compounds of the formula I, wherein

R^3 represents a hydrogen atom,

R^4 stands for a cyclopropyl group, a methoxy group or an amino group,

n has a value of 0,

m has a value of 0,

R^2 means an amino group,

A represents a hydrogen atom,

B means a hydrogen atom,

and pharmaceutically suitable acid addition salts thereof.

Another preferred subgroup of the compounds of the invention consists of the 8-methyl-7H-1,3-dioxolo/4,5-h//2,3/benzo-diazepine derivatives of the formula I, wherein

A forms together with B a valence bond between the carbon atoms in positions 8 and 9,

R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a morpholino group, wherein the phenyl group is optionally substituted by one or two C_{1-2} alkoxy group(s), or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 2 identical or different substituent(s) selected from the group consist droxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is optionally substituted by a halo atom or a C_{1-4} alkoxy group,

p has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group,

and pharmaceutically suitable acid addition salts thereof.

Within the latter subgroup, suitable 8-methyl-7H-1,3-dioxolo/4,5-h//2,3/benzo-diazepine derivatives are the following compounds of the formula I, wherein

A forms together with B a valence bond between the carbon atoms in positions 8 and 9,

R^2 represents a nitro group or an amino group,

R^1 stands for a group of the formula

$-CO-(CH_2)_p-R^6$, wherein

R^6 means a chloro atom, a phenoxy group, or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 represent, independently, a hydrogen atom, a guamyl group or a C_{1-3} alkyl group optionally substituted by a phenyl group, a dimethoxyphenyl group or a morpholino group, or

R^7 and R^8 form with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by one or two identical or different substituent(s) selected from the group consisting of a hydroxy group, a methoxyphenyl group, a fluorophenyl group, a benzyl group or a (methoxyphenoxy)-(hydroxypropyl) group,

p has a value of 0, 1 or 2,

and pharmaceutically suitable acid addition salts thereof.

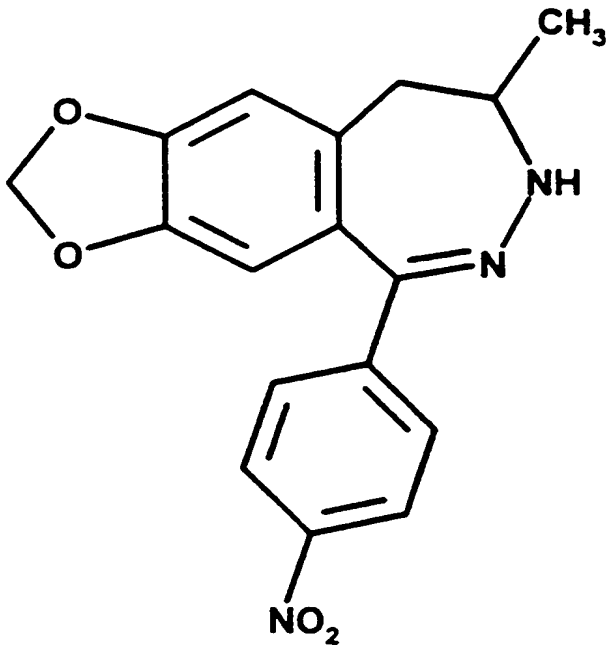
Within the latter subgroup, especially preferred 8-methyl-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine derivatives are the following compounds of the formula I, wherein

R^2 represents an amino group,

R^1, A and B are as defined in connection with the latter subgroup, and pharmaceutically suitable acid addition salts thereof.

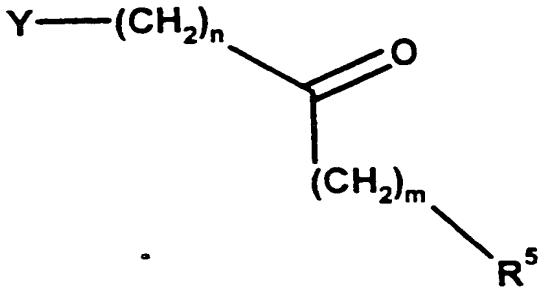
The 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives of the formula I are prepared as follows:

a) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for a halo atom or a pyridyl group, n has a value of 0, 1 or 2, m has a value of 0, 1 or 2, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H--1,3-dioxolo/4,5-h//2,3/benzodiazepine of the formula III



III

is reacted with a reagent of the formula VI



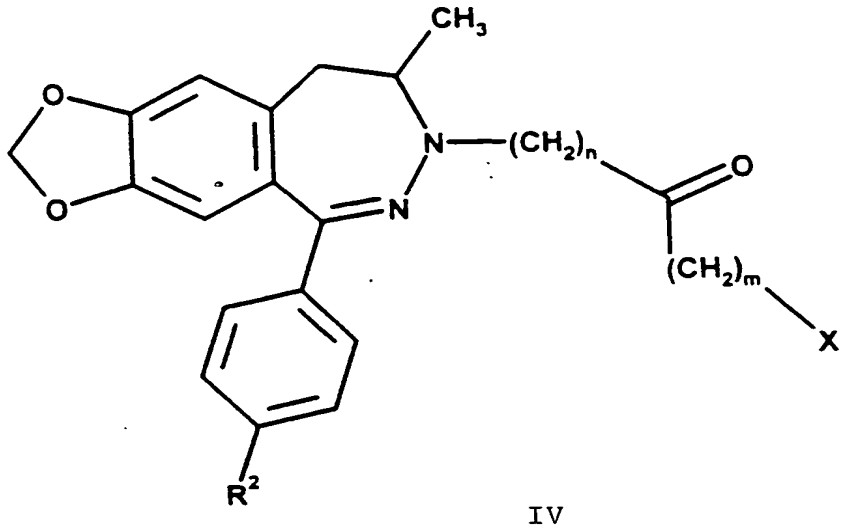
VI

wherein Y represents a leaving group, R^5 is a halo atom or a pyridyl group; or

b) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for an imidazolyl group, n has a value of O, m has a value of O, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine of the formula III is reacted with 1,1'-carbonyldiimidazole; or

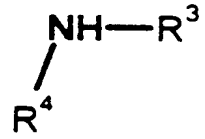
c) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for a group of the formula $-NR^3R^4$, wherein R^3, R^4, n and m are as defined in connection with formula I, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)--9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine of the formula III is reacted with a reagent of the formula VI, wherein Y and R^5 represent,

independently, a leaving group, n and m are as stated above, and the obtained benzodiazepine derivative of the formula IV



IV

wherein X stands for a leaving group, n and m are as stated above, is reacted with an amine of the formula VII

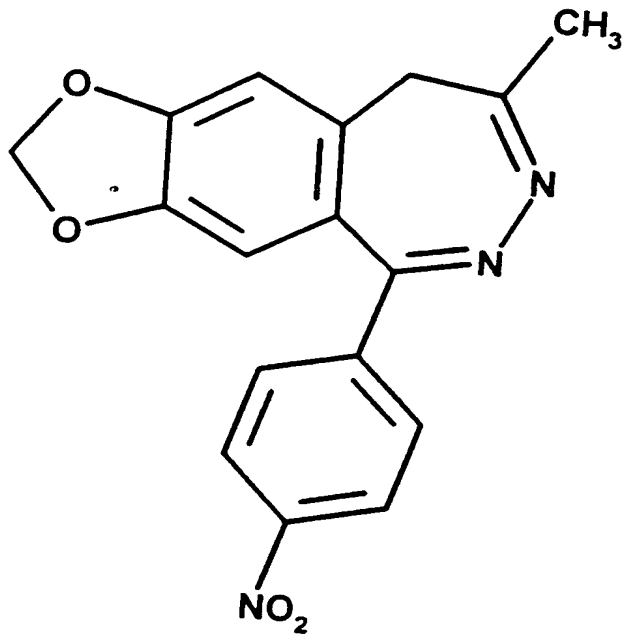


VII

wherein R^3 and R^4 are as stated above; or

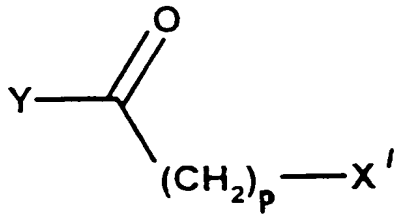
d) for the preparation of a compound of the formula I, wherein R^1 stands for a group of the formula $-CO-(CH_2)_p-R^6$, wherein R^6 represents a halo atom, a phenoxy group or a C_{1-4} alkoxy group, p has a value of 0, 1 or 2, A forms together with B a valence bond, R^2 means a nitro group, the 8-methyl-

-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine of the formula II



II

is reacted with an acylating agent of the formula IX

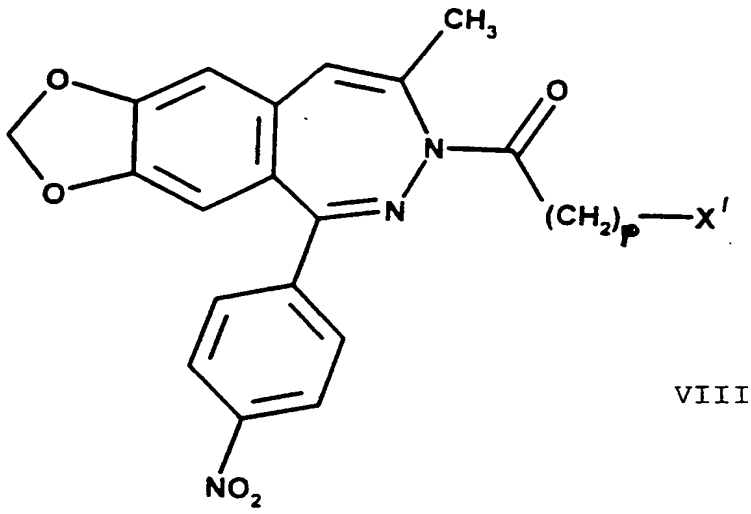


IX

wherein Y represents a leaving group, X' stands for a halo atom, a phenoxy group or a C_{1-4} alkoxy group, p has a value of 0, 1 or 2;
or

e) for the preparation of a compound of the formula I, wherein R^1 stands for a

group of the formula $-CO-(CH_2)_p-R^6$, wherein R^6 represents a group of the formula $-NR^7R^8$, wherein R^7, R^8 and p are as defined in connection with the formula I, A forms together with B a valence bond, R^2 means a nitro group, the 8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine of the formula II is reacted with an acylating agent of the formula IX, wherein each of Y and X' represents, independently, a leaving group, p is as stated above, and the obtained acylated compound of the formula VIII



VIII

wherein X' and p are as defined above, is reacted with an amine of the formula HNR^7R^8, wherein R^7 and R^8 are as stated above;

and, if desired, an obtained compound of the formula I, wherein R^2 represents a nitro group, R^1, A and B are as defined in connection with the formula I, is transformed

into a compound of the formula I, wherein R^2 stands for an amino group, by reduction;

and, if desired, an obtained compound of the formula I, wherein R^2 represents an amino group, R^1, A and B are as defined in connection with the formula I, is reacted with a C_{1-4} alkanecarboxylic acid or a reactive acylating derivative thereof;

and, if desired, an obtained base of the formula I is converted to a pharmaceutically suitable acid addition salt or liberated from the acid addition salt.

If a reagent of the formula VI, wherein n has a value of 0, is used, said reagent is an acylating agent such as a carboxylic halide, a carboxylic anhydride, a carbonate ester, carbonyldiimidazole, an omega-halo-carboxylic halide, an omega-halocarbonate ester etc. The acylation is carried out in the presence or absence of an acid binding agent and/or pyridine, at a temperature of -20 to +150 °C, in the presence or absence of an organic solvent.

If a reagent of the formula VI, wherein n has a value of 1 or 2, is used, said reagent is an alkylating agent, for example the corresponding halide. The alkylation is performed in the presence or absence of an acid binding agent, at a temperature of 20 to 200 °C, in the presence or absence of an organic solvent.

The reaction of the benzodiazepine

derivative of the formula IV and the amine of the formula VII is carried out in a manner known from the literature /Houben-Weyl: Methoden der Organischen Chemie, Band XI, Amine, G. Thieme Verlag, Stuttgart, 1957; S. Patai: The chemistry of amine group, Interscience Publishers, 1968/.

The acylation of the compound of the formula II with the acylating agent of the formula IX and the amination of the compound of the formula VIII with the amine of the formula HNR^7R^8 are performed in a similar manner as described above.

The nitro compounds of the formula I can be reduced in a manner known in itself to obtain the corresponding amino compound. The reduction can be carried out for example with tin(II) chloride or in the presence of a catalyst using a hydrogen source. For example, the catalyst can be Raney nickel, palladium or platinum oxide, the hydrogen source is, for example, hydrazine, hydrazine hydrate, formic acid, a trialkylammonium formate or an alkali metal formate.

If desired, a base of the formula I is reacted with an inorganic or organic acid to transform it into a pharmaceutically suitable acid addition salt, or the base of the formula I is liberated from the acid addition salt using a stronger base.

The starting compound 7,8-dihydro-8--methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-

/4,5-h//2,3/benzodiazepine of the formula III can be prepared by reducing 8-methyl--5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine of the formula II in an analogous manner as described in the literature /Houben-Weyl: Methoden der Organischen Chemie, Band IV, Reduktion, G. Thieme Verlag, Stuttgart, 1989/ or using the processes known from HU-P No. 186 760.

The compound of the formula II can be prepared by the process known from HU-P No. 191 702.

The reagents of the formulae VI and IX as well as the amines of the formulae VII and HNR^7R^8 are commercially available.

The pharmacological effect of the novel compounds of the formula I was studied by in vitro and in vivo methods. 8-Methyl-5--(4-aminophenyl)-9H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine (compound "A") known from HUP No. 191 698 and GB-P No. 2 162 184 was used as the reference substance.

<u>In vitro determination of AMPA antagonist effect</u>

PSI (inhibition of population spike) test

The field potentials (population spike) evoked by electric stimulation of the Shaffer collateral comissural pathway were measured in the CA1 neurones of rat hippocampus. The

population spike can be inhibited by AMPA/kainate antagonists. The non-cumulative IC_{50} values are shown in Table I. /Tarnawa, I., Molnár, P., Gaál, L., Andrási, F.: Inhibition of hippocampal field potentials by GYKI 52466 in vitro and in vivo, Acta Physiol. Hung., 79(2), 163-9 (1992)/.

SD (spreading depression) test

The method is based on the phenomenon of spreading depression evoked by kainate in isolated retinal preparation of the chicken. The formation of spreading depression is inhibited (delayed) by AMPA/kainate antagonists. /Sheardown M.J.: The triggering of spreading depression in the chicken retina: a pharmacological study, Brain Res., 607(1-2), 189-194 (1993)/. The obtained IC_{50} values are shown in Table I.

Table I

Results obtained in tests suitable for the determination of in vitro AMPA antagonist effect

Compound (No. of Example)	Percent inhibition of population spike (10 microM)	SD[a] IC_{50} in microM
16	100	1.3
17	95	1.5
19	95	no data
46	no data	6.5
61	no data	2.8
"A"	58	9.5

[a] Spreading depression test.

As shown in Table I, the inhibitory effects of the novel compounds are significantly higher than that of reference compound "A".

In vivo assays

Muscle relaxant effect

The assay was done according to Hoppe in male NMRI mice weighing 20 to 25 g, with 10 animals in each group /Hoppe, J.O., J. Pharmacol. Exp. Ther., 100, 333 (1950)/. Following the ip. treatment of animals, the number of mice showing muscle weakness were

recorded at every 10 minutes in the first hour and at half hour intervals afterwards. The animals falling off the 60^{o} inclined screen within 30 seconds were considered positive. ED_{50} values of the given compounds were determined at each time. The duration of effect was defined as the time of last reading when the effect was at least 30 %. The results obtained are summarized in Table II.

Table II
Muscle relaxant effect

Compound (No. of Example)	Muscle relaxant effect ED_{50} [x] ip. in mg/kg	duration in hr
16	21.1	higher than 2
17	18.1	4
"A"	24.5	1

[x] determined at the time of maximal effect.

Although the muscle relaxant activity of the novel compounds are about the same as that of reference compound "A", the duration of action is significantly longer as shown in Table II.

Maximal electroshock test (MES)

Male NMRI mice weighing 20 to 30 g were used for the method of Swinyard et al. /Swinyard, E.A., Brown, W.C. and Goodman, L.S.: Comparative assays of antiepileptic drugs in mice and rats, J. Pharmacol., 106, 319 (1952)/. The animals, 10 in each group, were treated ip. either with various doses of the test substance or with vehicle. After 30 minutes, a 50 Hz, 40 mA electroshock was applied for 0.4 s through corneal electrodes. The number of animals that developed tonic extensor convulsion of the hind-limbs was registered, percent inhibition was calculated, and ED_{50} values were determined by the method of Litchfield and Wilcoxon /Litchfield, J.T., Wilcoxon, F.A.: A simplified method of evaluating dose-effect experiments, J. Pharmacol. Exp. Ther., 96, 99 (1949)/ and summarized in Table III.

Audiogenic seizure (AS) test

The experiments were carried out by the slightly modified method of De Sarro et al. /De Sarro, G.B., Croucher, M.J. and Meldrum, B.S.: Anticonvulsant action of DS 103-282, Neuropharm., 23, 525 (1984)/. Groups of 8 male DBA/2j strain mice weighing 7 to 14 g were treated ip. with the test substance in 10 ml/kg volume. 15 minutes later, the animals

were placed into a covered glass container (30 cm in diameter) and exposed to a 14 kHz 120 dB tone for 60 s at the most. Seizure response was assessed using the following scale: 0 = normal behaviour, 1 = wild running, 2 = clonus, 3 = tonic flexor seizure, 4 = tonic extensor seizure. The maximum response during the 60 s exposure was recorded for each animal. Lethality was also noted. The ED_{50} values were determined by the method of Litchfield and Wilcoxon concerning the inhibition of clonic seizures and tonic extensor convulsions. The results are summarized in Table III.

Table III

Anticonvulsant effect following ip. treatment

Compound (No. of Example)	MES[x] ED_{50} in mg/kg	AS[xx] ED_{50} in mg/kg	
		tonic convulsion	clonic convulsion
16	4.6	1.6	2.5
17	3.7	no data	no data
"A"	6.9	3.6	4.3

[x] Inhibition of maximal electroshock.

[xx] Inhibition of sound induced seizure.

The novel compounds are significantly more

effective at the inhibition of maximal electroshock and audiogenic seizure than the reference compound "A" as shown in Table III.

The compound of Example 46 has an approximate anticonvulsive ED_{50} value of 10 mg/kg ip. in the MES test (not shown in Table III), while in 60 mg/kg dose it has no muscle relaxant effect in the inclined screen. In contrast, the anticonvulsive ED_{50} value of the reference compound "A" is 6.9 mg/kg, however, at about 4.5 times higher dose, the reference compound produces about 50 % muscle relaxant effect, and at 60 mg/kg dose all the treated animals showed muscle relaxation. Since strong muscle relaxation may seriously limit the therapeutic application of a drug, the lack of muscle relaxant effect of some novel compounds of the invention provides potential advantage over reference compound "A" in the clinical use.

Global ischemia induced by magnesium chloride

The experiments were carried out as described by Berga et al. /Berga, P., Beckett, P.R., Roberts, D.J., Llenas, J., Massingham, R.: Synergistic interactions between piracetam and dihydroergocristine in some animal models of cerebral hypoxia and ischemia, Arzneim.--Forsch., 36, 1314-1320 (1986)/. Groups of 10 male NMRI mice weighing 20 to 25 g were

treated ip. with the test substance in 10 mg/kg volume. After 30 minutes, saturated aqueous magnesium chloride solution was applied iv. (5 ml/kg) resulting in an immediate cardiac arrest. The elapsed time between the iv. injection and the last gasping was measured (gasping time). The means of the treated groups were expressed as percent of control. Statistical analysis was done by ANOVA followed by DUNCAN test. The dose resulting in 50 % descrease in gasping time (ID_{50}) was calculated by linear regression. The results are shown in Table IV.

Table IV

Increase in gasping time in the magnesium chloride induced global ischemia test in mice

Compound (No. of Example)	Dose in mg/kg ip.	Effect in %	ID_{50} in mg/kg ip.
16	30	61	13
17	30	52	27
"A"	30	55	30

From Table IV it can be seen that the novel compound of Example 16 is as effective at neuroprotection in 13 mg/kg dose as the reference compound "A" in 30 mg/kg dose.

Thus, the novel 8-substituted-9H--1,3-dioxolo/4,5-h//2,3/benzodiazepine derivatives of the formula I can be used as active ingredients of pharmaceutical compositions.

On the basis of the above test results, the novel compounds of the invention - due to their competitive AMPA/kainate antagonist property - have considerable muscle relaxant, neuroprotective and anticonvulsive effects. Consequently, the novel compounds can be used for the treatment of any disease such as epilepsy, diseases resulting in muscle spasm, neurodegenerative diseases, states after stroke, migraine and vomiting, wherein the inhibition of the AMPA/kainate receptors may have a favourable effect.

Some compounds of the invention which possess considerable anticonvulsive and neuroprotective activities, while they have no or weak muscle relaxant effect, can be primarily applied as antiepileptics. In the course of their application, the lack of muscle relaxant action provides notable benefit over the known AMPA/kainate antagonist 2,3-benzodiazepine derivatives.

The pharmaceutical compositions of the invention contain a therapeutically active amount of the compound of the formula I or a pharmaceutically suitable acid addition salt thereof and one or more conventional carrier(s).

The pharmaceutical compositions of the invention are suitable for peroral, parenteral or rectal administration or for local treatment, and can be solid or liquid.

The solid pharmaceutical compositions suitable for peroral administration may be powders, capsules, tablets, film-coated tablets, microcapsules etc., and can comprise binding agents such as gelatine, sorbitol, poly(vinylpyrrolidone) etc.; filling agents such as lactose, glucose, starch, calcium phosphate etc.; auxiliary substances for tabletting such as magnesium stearate, talc, poly(ethyleneglycol), silica etc.; wetting agents such as sodium laurylsulfate etc. as the carrier.

The liquid pharmaceutical compositions suitable for peroral administration may be solutions, suspensions or emulsions and can comprise e.g. suspending agents such as gelatine, carboxymethylcellulose etc.; emulsifiers such as sorbitane monooleate etc.; solvents such as water, oils, glycerol, propyleneglycol, ethanol etc.; preservatives such as methyl p-hydroxybenzoate etc. as the carrier.

Pharmaceutical compositions suitable for parenteral administration consist of sterile solutions of the active ingredient, in general.

Dosage forms listed above as well as other dosage forms are known per se, see e.g.

Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co., Easton, USA (1990).

The pharmaceutical compositions of the invention contain, in general, 0.1 to 95.0 per cent by mass of a compound of the formula I or a pharmaceutically suitable acid addition salt thereof. A typical dose for adult patients amounts to 0.1 to 20 mg of the compound of the formula I or a pharmaceutically suitable acid addition salt thereof, daily. The above dose can be administered in one or more portions. The actual dosage depends on many factors and is determined by the doctor.

The pharmaceutical compositions of the invention are prepared by admixing a compound of the formula I or a pharmaceutically suitableacid addition salt thereof to one or more carrier(s), and converting the mixture obtained to a pharmaceutical composition in a manner known per se. Useful methods are known from the literature, e.g. Remington's Pharmaceutical Sciences.

A preferred subgroup of the pharmaceutical compositions of the invention contains a 1,3--dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a chloro atom, a pyridyl

group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a cyclopropyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two methyl group(s) or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and the heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 methoxy groups, or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 methoxy groups, n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group, or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Within the above subgroup, the suitable pharmaceutical compositions of the invention

contain a 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

R^3 and R^4 represent, independently, a hydrogen atom, a cyclopropyl group, a methoxy group, an amino group, a dimethylaminophenyl group or a C_{1-2} alkyl group which latter is substituted by a phenyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl group, or

R^3 and R^4 form, together with the adjacent nitrogen atom and optionally a further nitrogen atom or oxygen atom, an imidazolyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl group,

n has a value of 0 or 1,

m has a value of 0 or 1,

R^2 stands for a nitro group or an amino group,

A represents a hydrogen atom,

B means a hydrogen atom,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Within the above subgroup, the especially preferred pharmaceutical compositions of the invention contain a 1,3-dioxolo/4,5-h//2,3/-benzodiazepine derivative of the formula I, wherein

R^3 represents a hydrogen atom,

R^4 stands for a cyclopropyl group, a methoxy group or an amino group,

n has a value of 0,

m has a value of 0,

R^2 means an amino group,

A represents a hydrogen atom,

B means a hydrogen atom,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Another preferred subgroup of the pharmaceutical compositions of the invention contains an 8-methyl-7H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine derivative of the formula I, wherein

A forms together with B a valence bond between the carbon atoms in positions 8 and 9,

R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a morpholino group, wherein the phenyl group is optionally substituted by one or two C_{1-2} alkoxy group(s), or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising

one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 2 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is optionally substituted by a halo atom or a C_{1-4} alkoxy group,

p has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Within the latter subgroup, the suitable pharmaceutical compositions of the invention contain an 8-methyl-7H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine derivative of the formula I, wherein

A forms together with B a valence bond between the carbon atoms in positions 8 and 9,

R^2 represents a nitro group or an amino group,

R^1 stands for a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 means a chloro atom, a phenoxy group, or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 represent, independently,

a hydrogen atom, a guamyl group or a C_{1-3} alkyl group optionally substituted by a phenyl group, a dimethoxyphenyl group or a morpholino group, or

R^7 and R^8 form with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by one or two identical or different substituent(s) selected from the group consisting of a hydroxy group, a methoxyphenyl group, a fluorophenyl group, a benzyl group or a (methoxyphenoxy)-(hydroxypropyl) group,

p has a value of 0, 1 or 2,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Within the latter subgroup, the especially preferred pharmaceutical compositions of the invention contain an 8-methyl-7H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

R^2 represents an amino group,

R^1, A and B are as defined above,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

Furthermore, the invention refers to a method of pharmaceutical treatment which comprises administering a therapeutically effective non-toxic amount of a 1,3-dioxolo-/4,5-h//2,3/benzodiazepine derivative of the formula I or a pharmaceutically suitable acid addition salt thereof to a patient suffering from especially epilepsy or a neurodegenerative disease or being in a state after stroke.

The invention is further elucidated, in detail, by means of the following Examples.

Example 1

(±)-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)-9H--1,3-dioxolo/4,5-h//2,3/benzodiazepine-7--carboxylic acid-imidazolide

3.25 g (10.0 mmoles) of (±)-7,8-dihydro--8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine and 1.95 g (12.0 mmoles) of 1,1'-carbonyldiimidazole are boiled in 75 cm^3 of anhydrous tetrahydrofuran for 20 hours. The reaction mixture is cooled with ice-water, the product precipitated is filtered, and washed with 50 cm^3 of diethyl ether.

Thus, 3.58 g (85 %) of the title compound are obtained. M.p.: 244-248 °C.
^1H NMR ($CDCl_3$): δ 8.26 (2H, d, J=9.0 Hz), 7.91 (1H, s), 7.75 (2H, d, J=9.0 Hz), 7.31 (1H, s), 7.04 (1H, s), 6.88 (1H, s), 6.53 (1H, s), 6.08 (1H, d, J=1.3 Hz), 6.05 (1H,

d, J=1.3 Hz), 5.24 (1H, m), 2.99 (1H, dd, J=14.5 and 4.8 Hz), 2.78 (1H, dd, J=14.6 and 10.2 Hz), 1.40 (3H, d, J=6.4 Hz).

Example 2

(±)-7,8-Dihydro-8-methyl-7-nicotinyl-5-(4--nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

3.25 g (10.0 mmoles) of (±)-7,8-dihydro-8-methyl-5-(4-nitrophenyl)--9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine are dissolved in 100 cm^3 of anhydrous dichloromethane, to the solution obtained, 2.43 g (3.25 cm^3, 24.0 mmoles) of triethylamine and, in small portions, 1.96 g (11.0 mmoles) of nicotinic acid hydrochloride are added. The reaction mixture is stirred at room temperature for 4 hours, then washed three times using 30 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 70 cm^3 of acetonitrile, and the crystals are washed with 15 cm^3 of diethyl ether.

Thus, 3.40 g (79 %) of the title compound are obtained. M.p.: 226-228 °C.
^{1}H NMR ($CDCl_3$): δ 8.66 (2H, m), 8.14 (2H, d, J=9.0 Hz), 7.83 (1H, dt, J=7.9 and 2.0 Hz), 7.45 (2H, d, J=9.0 Hz), 7.37 (1H, m), 6.86 (1H, s), 6.51 (1H, s), 6.08 (1H, d, J=1.3 Hz), 6.06 (1H, d, J=1.3 Hz), 5.47 (1H, m),

3.05 (1H, dd, J=14.4 and 4.2 Hz), 2.85 (1H, dd, J=14.4 and 9.6 Hz), 1.33 (3H, d, J=6.4 Hz).

Example 3

(±)-7,8-Dihydro-8-methyl-7-/N-(4-morpholino-ethyl)carbamoyl/-5-(4-nitrophenyl)-9H-1,3--dioxolo/4,5-h//2,3/benzodiazepine

2.09 g (5.0 mmoles) of the imidazolide derivative described in Example 1 are suspended in 100 cm^3 of dichloromethane, and, to the suspension, 1.44 g (1.44 cm^3, 11.0 mmoles) of (4-morpholinoethyl)amine are added. The reaction mixture is boiled for 10 hours, then washed three times using 30 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 85 cm^3 of acetonitrile, the crystals are washed with 10 cm^3 of diethyl ether.

Thus, 1.83 g (76 %) of the title compound are obtained. M.p.: 198-203 °C.
^1H NMR ($CDCl_3$): δ 8.24 (2H, d, J=8.9 Hz), 7.68 (2H, d, J=8.9 Hz), 7.07 (1H, t, J=5.0 Hz), 6.73 (1H, s), 6.47 (1H, s), 6.01 (1H, s), 6.01 (1H, s), 6.00 (1H, s), 5.45 (1H, m), 3.71 (4H, m), 3.42 (2H, m), 3.12 (1H, dd, J=14.6 and 2.1 Hz), 2.87 (1H, dd, J=14.7 and 6.6 Hz), 2.55 (2H, m), 2.49 (4H, m), 0.97 (3H, d, J=6.6 Hz).

Example 4

(±)-7-(N-Cyclopropylcarbamoyl)-7,8-dihydro-8--methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine

2.09 g (5.0 mmoles) of the imidazolide derivative described in Example 1 are boiled in 30 cm^3 of cyclopropylamine for 4 hours, then the amine is distilled off under reduced pressure. The residue is taken up in 75 cm^3 of dichloromethane, washed three times using 30 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 50 cm^3 of ethanol, and washed with 10 cm^3 of diethyl ether.

Thus, 1.59 g (78 %) of the title compound are obtained. M.p.: 198-203 °C.
^{1}H NMR /$(CD_3)_2SO$/: δ 8.23 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.(Hz), 6.99 (1H, s), 6.85 (1H, d, J=2.8 Hz), 6.48 (1H, s), 6.07 (2H, s), 5.20 (1H, m), 3.00 (1H, dd, J=14.5 and 2.1 Hz), 2.86 (1H, dd, J=14.5 and 7.2 Hz), 2.60 (1H, m), 0.90 (3H, d, J=6.4 Hz), 0.63 (2H, m), 0.53 (2H, m).

Example 5

(±)-7,8-Dihydro-8-methyl-7-(N-methoxy-carbamoyl)-5-(4-nitrophenyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine

2.03 g (25.0 mmoles) of methoxyamine

hydrochloride and 3.45 g (25.0 mmoles) of potassium carbonate are stirred in 75 cm^3 of anhydrous dimethylformamide for half an hour, then, 2.09 g (5.0 mmoles) of the imidazolide derivative described in Example 1 are added. The reaction mixture is stirred for 6 hours, then the solvent is evaporated at a pressure of 55 Pa. The residue is suspended in 100 cm^3 of water, stirred for half an hour, filtered, washed with 50 cm^3 of water, and dried. The crude product is recrystallized from 35 cm^3 of tetrahydrofuran, and washed with 10 cm^3 of diethylether.

Thus, 2.30 g (68 %) of the title compound are obtained. M.p.: 156-162 °C.
^{1}H NMR /$(CD_3)_2SO$/: δ 10.00 (1H, s), 8.24 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz), 7.03 (1H, s), 6.51 (1H, s), 6.09 (1H, s), 6.08 (1H, s), 5.08 (1H, m), 3.63 (3H, s), 3.02 (1H, dd, J=14.4 and 3.5 Hz), 2.81 (1H, dd, J=14.4 and 8.2 Hz), 0.99 (3H, d, J=6.4 Hz).

Example 6

(±)-7,8-Dihydro-8-methyl-7-[N-/1-(2-methoxy-phenyl)-4-piperazinylethyl/carbamoyl]-5--(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

3.86 g (11.0 mmoles) of 1-(2-methoxy-phenyl)-4-piperazinylethyl ammonium fumarate and 3.04 g (22.0 moles) of potassium carbonate are stirred in a mixture of 75 cm^3 of

dichloromethane and 75 cm^3 of water at room temperature for half an hour. The phases are separated, and the aqueous phase is extracted twice with 30 cm^3 of dichloromethane each time. The combined organic phases are washed with 30 cm^3 of water, and dried over anhydrous magnesium sulfate. To the thus-obtained solution, 2.09 g (5.0 mmoles) of the imidazolide derivative described in Example 1 are added, the mixture is stirred at room temperature for 24 hours, then washed three times using 30 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 55 cm^3 of acetonitrile, and washed with 10 cm^3 of diethyl ether.

Thus, 2.17 g (74 %) of the title compound are obtained. M.p.: 238-242 °C.
^1H NMR ($CDCl_3$): δ 8.22 (2H, d, J=8.8 Hz), 7.69 (2H, d, J=8.8 Hz), 7.19 (1H, t, J=4.8 Hz), 7.01 (3H, m), 6.91 (1H, m), 6.73 (1H, s), 6.46 (1H, s), 5.99 (1H, s), 5.98 (1H, s), 5.45 (1H, m), 3.87 (3H, s), 3.46 (2H, m), 3.10 (5H, m), 2.85 (1H, dd, J=14.8 and 6.4 Hz), 2.70 (4H, m), 2.63 (2H, m), 0.98 (3H, d, J=6.6 Hz).

Example 7

(±)-7-(N-Aminocarbamoyl)-7,8-dihydro-8-methyl--5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

2.09 g (5.0 mmoles) of the imidazolide derivative described in Example 1 are suspended in 75 cm^3 of dichloromethane. To the suspension, 1.25 g (1.21 cm^3, 25.0 mmoles) of 98-100 % hydrazine hydrate are added. The reaction mixture is stirred at room temperature for 10 hours, then washed three times using 30 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The crude product is crystallized from 45 cm^3 of ethanol, and the crystals are washed with 10 cm^3 of diethyl ether.

Thus, 1.04 g (54 %) of the title compound are obtained. M.p.: 219-220 °C.
^1H NMR ($CDCl_3$): δ 8.23 (2H, d, J=9.0 Hz), 7.62 (2H, d, J=9.0 Hz), 7.52 (1H, broad s), 6.73 (1H, s), 6.45 (1H, s), 6.01 (1H, d, J=1.3 Hz), 6.00 (1H, d, J=1.3 Hz), 5.38 (1H, m), 3.82 (2H, broad s), 3.12 (1H, dd, J=14.8 and 2.0 Hz), 2.86 (1H, dd, J=14.8 and 6.5 Hz), 0.99 (3H, d, J=6.6 Hz).

Example 8

(±)-2-/-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)--9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine--7-yl/-N-(2,6-dimethylphenyl)acetamide

A mixture of 9.80 g (30.0 mmoles) of (±)-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)--9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine and 7.10 g (36.0 mmoles) of 2-chloro-N-(2,6--dimethylphenyl)acetamide is heated at 140

^{o}C for 2 hours, then at 160 ^{o}C again for 2 hours. The reaction mixture is cooled back and dissolved in 200 cm^3 of chloroform. The organic phase is washed with 50 cm^3 of 10 % aqueous sodium hydroxide and 100 cm^3 of water, dried over anhydrous magnesium sulfate, and evaporated. The evaporation residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063 mm) using a mixture of hexane and acetone as the eluent.

Thus, 4.38 g (30 %) of the title compound are obtained. M.p.: 172-174 ^{o}C.
^{1}H NMR ($CDCl_3$): δ 8.22 (2H, d, J=9.1 Hz), 7.82 (2H, d, J=9.1 Hz), 7.65 (1H, s), 7.03 (3H, s), 6.86 (1H, s), 6.45 (1H, s), 6.02 (2H, bs), 4.15 (1H, d, J=16.8 Hz), 4.05 (1H, m), 3.96 (1H, d, J=16.8 Hz), 2.96 (1H, dd, J=14.0 Hz, J= 5.8 Hz), 2.48 (1H, dd, J=14.0 Hz, J=4.3 Hz), 2.07 (6H, s), 1.3 (3H, d, J=6.2 Hz).

Example 9
(±)-2-/-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)--9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine--7-yl/acetamide

9.80 g (30.0 mmoles) of (±)-7,8-dihydro--8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine and 3.40 g (36 mmoles) of 2-chloroacetamide are heated at 160 ^{o}C for 6 hours. The reaction mixture is cooled back, and dissolved in 200 cm^3 of

chloroform. The organic phase is washed with 50 cm^3 of 10 % aqueous sodium hydroxide and 100 cm^3 of water, dried over anhydrous magnesium sulfate, and evaporated. The evaporation residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063 mm) using a mixture of hexane and acetone as the eluent.

Thus, 3.30 g (29 %) of the title compound are obtained. M.p.: 216-218 °C.
^{1}H NMR ($CDCl_3$): δ 8.20 (2H, d, J=9.1 Hz), 7.66 (2H, d, J=9.1 Hz), 7.07 (1H, s), 6.97 (1H, s), 6.87 (1H, s), 6.54 (1H, s), 6.06 (2H, s), 4.10 (1H, m), 3.91 (1H, d, J=16.8 Hz), 3.79 (1H, d, J=16.8 Hz), 3.05 (1H, dd, J=14.0 Hz, J=3.4 Hz), 2.59 (1H, dd, J=14.0 Hz, J=5.2 Hz), 0.97 (3H, d, J=6.2 Hz).

Example 10
(±)-7,8-Dihydro-7-(2-chloroacetyl)-8-methyl--5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

9.80 g (30.0 mmoles) of (±)-7,8-Dihydro-8-methyl-5-(4-nitrophenyl)--9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine are boiled with 20 cm^3 of 2-chloroacetyl chloride for 30 minutes, then the reaction mixture is evaporated, and the residue is suspended in 100 cm^3 of diethyl ether. The crystals obtained are filtered, and washed with 20 cm^3 of diethyl ether.

Thus, 11.22 g (93) of the title compound are obtained. M.p.: 220-222 °C.
^{1}H NMR ($CDCl_3$): δ 8.27 (2H, d, J=9.0 Hz), 7.73 (2H, d, J=9.0 Hz), 6.77 (1H, s), 6.47 (1H, s), 6.03 (2H, s), 5.35 (1H, m), 4.57 (1H, d, J=13.8 Hz), 4.47 (1H, d, J=13.8 Hz), 3.08 (1H, dd, J=14.6 Hz, J=3.2 Hz), 2.82 (1H, dd, J=14.6 Hz, J=8.0 Hz), 1.06 (3H, d, J=6.6 Hz).

Example 11

(±)-7,8-Dihydro-8-methyl-7-[3-/4-(2-methoxyphenyl)piperazinyl/propionyl]-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 6.40 g (16.0 mmoles) of (±)-7,8-dihydro-7-(2-chloroacetyl)-8-methyl--5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine, 7.68 g (40.0 mmoles) of 4-(2-methoxyphenyl)piperazine and 32 cm^3 of acetonitrile is boiled for 30 minutes. Then, the reaction mixture is evaporated. To the evaporation residue, 50 cm^3 of water are added, the crystals obtained are filtered, and washed with 10 cm^3 of water.

Thus, 7.90 g (89 %) of the title compound are obtained. M.p.: 175-176 °C.

Example 12

(±)-7,8-Dihydro-8-methyl-7-morpholinoacetyl--5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine

A mixture of 6.00 g (15.0 mmoles) of (+)-7,8-dihydro-7-(2-chloroacetyl)-8-methyl--5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine, 3.00 g (36.0 mmoles) of morpholine and 30 cm^3 of acetonitrile is boiled for 2 hours. Then, the reaction mixture is evaporated. To the evaporation residue, 100 cm^3 of diethyl ether are added, the crystals obtained are filtered, and recrystallized from a mixture of 2-propanol and water.

Thus, 4.90 g (73 %) of the title compound are obtained. M.p. 206-208 °C.

Example 13

(±)-7-[2-/N-Benzyl-N-(2-morpholinoethyl)-amino/acetyl]-7,8-dihydro-8-methyl-5-(4--nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

A mixture of 4.00 g (10.0 mmoles) of (±)-7,8-dihydro-7-(2-chloroacetyl)-8-methyl--5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine, 5.50 g (25.0 mmoles) of N-benzyl-N-(2-morpholinoethyl)amine and 20 cm^3 of acetonitrile is boiled for 1 hour. Then, the reaction mixture is evaporated. To the evaporation residue, 50 cm^3 of diethyl ether are added, and the crystals obtained are filtered. The mother liquor is evaporated, and the evaporation residue is subjected to chromatography over silica gel (Kieselgel

G, 0.2-0.063 mm) using a mixture of chloroform and methanol as the eluent.

Thus, 5.10 g (87 %) of the title compound are obtained as an oil.

^{1}H NMR ($CDCl_3$): δ 8.22 (2H, d, J=9.0 Hz), 7.61 (2H, d, J=9.0 Hz), 7.3 (5H, m), 6.75 (1H, s), 6.44 (1H, s), 6.02 (2H, s), 5.40 (1H, m), 3.93 (1H, d, J=17.5 Hz), 3.92 (2H, s), 3.77 (1H, d, J=17.5 Hz), 3.66 (4H, t, J=4.7 Hz), 3.04 (1H, dd, J=14.6 Hz, J=2.9 Hz), 2.92 (2H, t, J=7.1 Hz), 2.78 (1H, dd, J=14.6 Hz, J=11.8 Hz), 2.49 (2H, t, J=7.1 Hz), 2.39 (4H, t, J=4.7 Hz), 1.06 (3H, d, J=6.6 Hz).

Examples 14 to 19

A general process for reducing the nitro group of the compounds described in Examples 2 to 7 by catalytical hydrogenation

5.0 mmoles of the nitro compound are dissolved in a mixture of 100 cm^3 of dichloromethane and 100 cm^3 of methanol, and the solution is hydrogenized in the presence of 0.10 g of 10 % palladium/carbon catalyst at room temperature and 5.065×10^5 Pa pressure. Following the hydrogenization, the catalyst is filtered, the solvent is evaporated under reduced pressure, and the crude product is recrystallized. The following compounds are obtained:

Example 14

(±)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl-7--nicotinyl-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

Solvent for crystallization: toluene.
M.p.: 221-223 °C.
Yield: 61 %.
Analysis: for $C_{23}H_{20}N_4O_3$ (400.44)
calculated: C 68.99 %, H 5.03 %, N 13.99 %;
found: C 69.53 %, H 5.16 %, N 13.56 %.
^{1}H NMR /$CDCl_3$ + $(CD_3)_2SO$, 70 °C/: δ 8.54 (1H, dd, J=4.8 and 1.5 Hz), 8.49 (1H, m), 7.65 (1H, m), 7.31 (1H, dd, J=7.8 and 4.8 Hz), 7.11 (2H, d, J=8.5 Hz), 6.70 (1H, s), 6.57 (1H, s), 6.53 (2H, d, J=8.5 Hz), 6.03 (1H, s), 6.01 (1H, s), 5.21 (1H, m), 5.09 (2H, s), 2.81 (1H, dd, J=13.9 and 5.6 Hz), 2.63 (1H, t, J=13.5 Hz), 1.37 (3H, d, J=6.0 Hz).

Example 15

(±)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl--7-/N-(4-morpholinoethyl)carbamoyl/-9H--1,3-dioxolo/4,5-h//2,3/- benzodiazepine

Solvent for crystallization: dichloromethane.
M.p.: 262-264 °C.
Yield: 66 %.
Analysis: for $C_{24}H_{29}N_5O_4$ (451.53)
calculated: C 63.84 %, H 6.47 %, N 15.51 %;
found: C 63.96 %, H 6.41 %, N 15.30 %.
^{1}H NMR /$(CD_3)_2SO$/: δ 7.41 (2H, d, J=8.6 Hz),

6.98 (1H, s), 6.65 (2H, d, J=8.6 Hz), 6.54 (1H, s), 6.40 (1H, t, J=5.3 Hz), 6.06 (1H, s), 6.03 (1H, s), 5.50 (2H, broad s), 4.87 (1H, m), 3.64 (4H, m), 3.22 (2H, m), 2.83 (1H, dd, J=13.8 and 5.2 Hz), 2.42 (7H, m), 1.10 (3H, d, J=6.2 Hz).

Example 16

(±)-5-(4-Aminophenyl)-7-(N-cyclopropyl-carbamoyl)-7,8-dihydro-8-methyl-9H-1,3--dioxolo/4,5-h//2,3/benzodiazepine

Solvent for crystallization: ethanol.
M.p.: 158-160 °C.
Yield: 72 %.
Analysis: for $C_{21}H_{22}N_4O_3$ (378.43)
calculated: C 66.65 %, H 5.85 %, N 14.80 %;
found: C 65.96 %, H 6.09 %, N 14.52 %.
^{1}H NMR /$(CD_3)_2SO$/: δ 7.38 (2H, d, J=8.4 Hz), 6.98 (1H, s), 6.57 (2H, d, J=8.4 Hz), 6.53 (1H, s), 6.13 (1H, d, J=3.0 Hz), 6.06 (1H, s), 6.02 (1H, s), 5.68 (2H, broad s), 4.80 (1H, m), 2.78 (1H, dd, J=13.5 and 5.6 Hz), 2.50 (1H, m), 2.35 (1H, t, J=12.7 Hz), 1.07 (3H, d, J=6.1 Hz), 0.55 (2H, m), 0.45 (2H, m).

Example 17

(±)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl--7-(N-methoxycarbamoyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine

Solvent for crystallization: ethanol.
M.p.: 159-162 °C.
Yield: 75 %.
Analysis: for $C_{19}H_{20}N_4O_4$ (368.40)
calculated: C 61.95 %, H 5.47 %, N 15.21 %;
found: C 61.62 %, H 5.56 %, N 15.32 %.
^1H NMR ($CDCl_3$): δ 9.23 (1H, s), 7.46 (2H, d, J=8.7 Hz), 6.99 (1H, s), 6.56 (2H, d, J=8.7 Hz), 6.53 (1H, s), 6.07 (1H, d, J=1.0 Hz), 6.03 (1H, d, J=1.0 Hz), 5.68 (2H, broad s), 4.75 (1H, m), 3.53 (3H, s), 2.79 (1H, dd, J=13.7 and 5.7 Hz), 2.36 (1H, dd, J=13.5 and 12.0 Hz), 1.12 (3H, d, J=6.1 Hz).

Example 18

(±)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl--7-[N-/1-(2-methoxyphenyl)-4-piperazinyl-ethyl/carbamoyl]-9H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine

Solvent for crystallization: diethyl ether.
M.p.: 121-130 °C.
Yield: 81 %.
Analysis: for $C_{31}H_{36}N_6O_4$ (556.67)
calculated: C 66.89 %, H 6.52 %, N 15.11 %;
found: C 66.52 %, H 6.68 %, N 15.02 %.
^1H NMR ($CDCl_3$): δ 7.46 (2H, d, J=8.4 Hz), 6.96 (3H, m), 6.88 (1H, d, J=8.0 Hz), 6.73 (1H, s), 6.67 (1H, t, J=4.8 Hz), 6.60 (2H, d, J=8.4 Hz), 6.59 (1H, s), 5.95 (1H, d, J=1.3 Hz), 5.93 (1H, d, J=1.3 Hz), 5.16 (1H, m), 3.87 (5H, broad s), 3.44 (1H, m), 3.37 (1H,

m), 3.16 (4H, m), 2.84 (1H, dd, J=14.0 and 4.4 Hz), 2.70 (4H, m), 2.65 (1H, dd, J=14.0 and 10.0 Hz), 2.58 (2H, m), 1.17 (3H, d, J=6.4 Hz).

Example 19

(±)-5-(4-Aminophenyl)-7-(N-aminocarbamoyl)--7,8-dihydro-8-methyl-9H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine

Solvent for crystallization: acetonitrile.
M.p.: 160-170 °C.
Yield: 64 %.
Analysis: for $C_{18}H_{19}N_5O_3$ (353.38)
calculated: C 61.18 %, H 5.42 %, N 19.82 %;
found: C 59.68 %, H 5.37 %, N 19.32 %.
^1H NMR ($CDCl_3$): δ 7.42 (2H, d, J=8.6 Hz), 7.07 (1H, s), 6.99 (1H, s), 6.56 (2H, d, J=8.6 Hz), 6.53 (1H, s), 6.07 (1H, d, J=0.8 Hz), 6.03 (1H, d, J=0.8 Hz), 5.68 (2H, s), 4.78 (1H, m), 3.96 (2H, s), 2.78 (1H, dd, J=13.7 and 5.7 Hz), 2.37 (1H, t, J=12.2 Hz), 1.11 (3H, d, J=6.2 Hz).

Example 20

(±)-2-/5-(4-Aminophenyl)-7,8-dihydro-8-methyl--1,3-dioxolo/4,5-h//2,3/benzodiazepine-7--yl/-N-(2,6-dimethylphenyl)acetamide

2.20 g (4.5 mmoles) of (±)-2-/7,8-dihydro--8-methyl5-(4-nitrophenyl)-1,3-dioxolo-/4,5-h//2,3/benzodiazepine-7-yl/-N-(2,6-

-dimethylphenyl)acetamide are dissolved in 22 cm^3 of ethanol, to the solution obtained, 0.22 g 10 % palladium/carbon catalyst suspended in 0.5 cm^3 of water are added. To the reaction mixture, a solution of 1.80 g (21.4 mmoles) of potassium formate in 1.8 cm^3 of water is added, drop by drop. The reaction mixture is stirred at room temperature for 4 hours, then the catalyst is filtered, the solvent is evaporated under reduced pressure, and the crude product is recrystallized from 2-propanol.

Thus, 0.90 g (44 %) of the title compound are obtained. M.p.: 219-221 °C.
Analysis: for $C_{27}H_{28}N_4O_5$ (456.55)
calculated: N 12.33 %;
found: N 11.85 %.
^1H NMR (DMSO-d_6): δ 8.01 (1H, s), 7.26 (2H, d, J=8.5 Hz), 7.0 (4H, m), 6.54 (2H, d, J=8.5 Hz), 6.46 (1H, s), 6.02 (2H, s), 5.52 (2H, s), 3.80 (1H, m), 3.76 (1H, d, J=15.6 Hz), 3.64 (1H, d, J=15.6 Hz), 2.78 (1H, dd, J=13.2 Hz, J=6.2 Hz), 2.35 (1H, dd, J=13.2 Hz, J=5.8 Hz), 1.96 (6H, s), 1.16 (3H, d, J=6.1 Hz).

Example 21

(±)-2-/5-(4-Aminophenyl)-7,8-dihydro-8-methyl--1,3-dioxolo/4,5-h//2,3/benzodiazepine-7--yl/-acetamide

A mixture of 1.52 g (4.0 mmoles) of (±)-2-/7,8-dihydro-8-methyl-5-(4-nitrophenyl)-

-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-acetamide, 3.60 g (16.0 mmoles) of tin(II) chloride dihydrate and 60 cm^3 of methanol is boiled for 8 hours, then, further 1.00 g (4.4 mmoles) of tin(II) chloride dihydrate are added to the reaction mixture, and boiling is continued for another 2 hours. The reaction mixture is evaporated, and, to the evaporation residue, 40 cm^3 of water and 40 cm^3 of chloroform are added. The aqueous phase is extracted still twice with 40 cm^3 of chloroform each time. To the aqueous phase, a solution of 4 g of sodium hydroxide in 20 cm^3 of water are added, and the mixture is extracted twice using 40 cm^3 of chloroform each time. The organic phase is washed twice with 30 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated. The evaporation residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063) using a mixture of hexane and acetone as the eluent.

Thus, 0.95 g (68 %) of the title compound are obtained. M.p.: 221-223 °C.
^1H NMR (DMSO-d_6): δ 7.22 (2H, d, J=8.7 Hz), 6.99 (1H, s), 6.95 (1H, d, J=3.6 Hz), 6.54 (1H, s), 6.53 (2H, d, J=8.7 Hz), 6.04 (2H, s), 5.94 (1H, d, J=3.6 Hz), 5.48 (2H, s), 3.66 (1H, m), 3.48 (1H, d, J=16.2 Hz), 3.41 (1H, d, J=16.2 Hz), 2.70 (1H, dd, J=5.7, J=13.5 Hz), 2.30 (1H, dd, J=5.7 Hz, J=13.5 Hz), 1.07 (3H, d, J=6.1 Hz).

Example 22

(±)-2-/5-(4-Aminophenyl)-7,8-dihydro-8-methyl--7-[3-/4-(2-methoxyphenyl)piperazinyl/-propionyl]-1,3-dioxolo/4,5-h//2,3/-benzodiazepine-7-yl/-acetamide

A mixture of 8.36 g (15.0 mmoles) of (±)-2-/7,8-dihydro-8-methyl-7-[3-/4-(2--methoxyphenyl)piperazinyl/propionyl]-5--(4-nitrophenyl)-1,3-dioxolo/4,5-h//2,3/-benzodiazepine, 20.40 g (90.0 mmoles) of tin(II) chloride dihydrate and 150 cm^3 of methanol is boiled for 1 hour. The reaction mixture is evaporated, and, to the evaporation residue, 200 cm^3 of water and 100 cm^3 of chloroform are added. The aqueous phase is extracted still twice with 100 cm^3 of chloroform each time. Then, to the aqueous phase, a solution of 25 g of sodium hydroxide in 150 cm^3 of water are added, and the aqueous phase is extracted three times using 150 cm^3 of chloroform each time. The organic phase is washed twice with 150 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated. The evaporation residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063 mm) using a mixture of chloroform and methanol as the eluent.

Thus, 4.36 g (55 %) of the title compound are obtained. M.p.: 253-254 °C.

Analysis: for $C_{30}H_{33}N_5O_4$ (527.63)

calculated: C 68.29 %, H 6.30 %, N 13.27 %;

found: C 57.89 %, H 6.27 %, N 13.31 %.
^{1}H NMR ($CDCl_3$): δ 7.51 (2H, d, J=8.7 Hz), 6.92 (4H, m), 6.76 (1H, s), 6.68 (2H, d, J=8.7 Hz), 6.60 (1H, s), 6.00 (1H, s), 5.95 (1H, s), 5.22 (1H, m), 4.1 (2H, s), 3.84 (3H, s), 3.45 (1H, m), 3.15 (1H, d, J=15.6 Hz), 3.08 (4H, m), 2.65 (6H, m), 1.32 (3H, d, J=6.4 Hz).

Example 23

(±)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl--7-[3-/4-(2-methoxyphenyl)piperazinyl/-propionyl]-1,3-dioxolo/4,5-h//2,3/-benzodiazepine difumarate dihydrate

1.63 g (3.0 mmoles) of (+)-5-(4-aminophenyl)-7,8-dihydro-8-methyl-7-[3-/4-(2--methoxyphenyl)piperazinyl/propionyl]-1,3-dioxolo/4,5-h//2,3/benzodiazepine and 0.7 g (6 mmoles) of fumaric acid are boiled in a mixture of 60 cm^3 of ethanol and 90 cm^3 of dichloromethane for 30 minutes. The hot reaction mixture is filtered, evaporated, and the residue is suspended in 50 cm^3 of diethyl ether. The crystals are filtered.

Thus, 1.75 g (73 %) of the title compound are obtained. M.p.: 162-164 °C.
Analysis: for $C_{38}H_{45}N_5O_{14}$ (795.81)
calculated: C 57.35 %, H 5.70 %, N 8.80 %;
found: C 57.25 %, H 5.67 %, N 8.84 %.
^{1}H NMR (DMSO-d_6): δ 7.38 (2H, d, J=8.7 Hz), 7.01 (1H, s), 6.92 (2H, m), 6.84 (2H, m),

6.62 (7H, m), 6.07 (1H, s), 6.06 (1H, s), 4.95 (1H, m), 3.75 (3H, s), 3.34 (1H, d, J=13.5 Hz), 3.22 (1H, d, J=13.5 Hz), 2.90 (4H, m), 2.80 (1H, dd, J=5.3 Hz, J=13.6 Hz), 2.63 (4H, m), 2.47 (1H, m), 1.18 (3H, d, J=6.2 Hz).

Example 24

(±)-5-(4-Aminophenyl)-7,8-dihydro-8-methyl--7-morpholinoacetyl-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

5.00 g (11.0 mmoles) of (±)-7,8-Dihydro--8-methyl-7-morpholinoacetyl-5-(4-nitrophenyl)--9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine are dissolved in 50 cm^3 of ethanol. To the solution, 0.50 g of 10 % palladium/carbon catalyst suspended in 1.0 cm^3 of water are added. Then, to the reaction mixture, a solution of 4.00 g (47.6 mmoles) of potassium formate in 4.0 cm^3 of water are added, drop by drop. The reaction mixture is stirred at room temperature for 2 hours, then again a solution of 2.00 g (23.8 mmoles) of potassium formate in 2.0 cm^3 of water are added, drop by drop. After further 2 hours' stirring, the catalyst is filtered, washed with a large quantity of ethanol, the solvent is evaporated under reduced pressure, and the residue is suspended in 100 cm^3 of diethyl ether. The crystals obtained are filtered, and the crude product is recrystallized from a mixture of acetonitrile and water.

Thus, 3.00 g (65 %) of the title compound are obtained. M.p.: 254-256 °C.
Analysis: for $C_{23}H_{26}N_4O_4$ (422.49)
calculated: N 13.26 %, H 6.20 %;
found: N 13.12 %, H 6.48 %.
^{1}H NMR ($CDCl_3$): δ 7.49 (2H, d, J=8.6 Hz), 6.75 (1H, s), 6.68 (2H, d, J=8.6 Hz), 6.58 (1H, s), 6.00 (1H, s), 5.97 (1H, s), 5.19 (1H, m), 4.1 (2H, bs), 3.69 (4H, t, J=4.6 Hz), 3.36 (1H, d, J=15.8 Hz), 3.07 (1H, d, J=15.8 Hz), 2.64 (2H, m), 2.53 (4H, m), 1.30 (3H, d, J=6.4 Hz).

Example 25

(±)-5-(4-Aminophenyl)-7-[2-/N-benzyl-N-(2-morpholinoethyl)amino/acetyl]-7,8-dihydro-8-methyl-9H-1,3-dioxolo/4,5h//2,3/-benzodiazepine

5.10 g (8.7 mmoles) of 7-[2-/N-benzyl-N-(2-morpholinoethyl)amino/acetyl]-7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5h//2,3/benzodiazepine are dissolved in 120 cm^3 of methanol. To the solution, 1.30 g of 10 % palladium/carbon catalyst suspended in 11 cm^3 of water are added, and, to the reaction mixture, 7.70 cm^3 (15.8 mmoles) of hydrazine hydrate are added, drop by drop. The reaction mixture is stirred at room temperature for 24 hours, then further 2.00 cm^3 (4.1 mmoles) of hydrazine hydrate are added. After further 48 hours' stirring, the

catalyst is filtered, washed with a large quantity of methanol, the solvent is evaporated under reduced pressure, and the residue is subjected to chromatography over silica gel (Kieselgel G, 0.2-0.063 mm) using a mixture of acetone and hexane as the eluent.

Thus, 3.70 g (77 %) of the title compound are obtained. M.p.: 68-70 °C.
Analysis: for $C_{32}H_{37}N_5O_4$ (555.683)
calculated: N 12.60 %, H 6.71 %;
found: N 12.16 %, H 6.93 %.
^1H NMR ($CDCl_3$): δ 7.43 (2H, d, J=8.7 Hz), 7.25 (5H, m), 6.76 (1H, s), 6.64 (2H, d, J=8.7 Hz), 6.51 (1H, s), 6.01 (1H, s), 5.97 (1H, s), 5.20 (1H, m), 3.99 (2H, bs), 3.84 (2H, s), 3.68 (1H, d, J=16.8 Hz), 3.63 (4H, t, J=4.6 Hz), 3.25 (1H, d, J=16.8 Hz), 2.82 (2H, m), 2.65 (2H, m), 2.43 (2H, m), 2.36 (4H, m), 1.26 (3H, d, J=6.2 Hz).

Example 26

Phenyl 8-methyl-5-(4-nitrophenyl)-7H-1,3--dioxolo/4,5-h//2,3/benzodiazepine-7--carboxylate

20.0 g (61.9 mmoles) of 8-methyl-5-(4--nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine are added to 600 cm^3 of chloroform, and, to the mixture, 37.2 g (237.6 mmoles) of phenyl chloroformate are added, drop by drop, at 5 to 10 °C in 15 minutes. The suspension is boiled for 7 hours, while

the mixture becomes a clear solution. After cooling, the solution is evaporated under reduced pressure, to the evaporation residue, 300 cm^3 of diethyl ether are added, and the mixture is stirred at 25 °C for 16 hours. The crystals obtained are filtered, and washed three times using 50 cm^3 of diethyl ether each time.

Thus, 26.0 g (94.9 %) of the title compound are obtained. M.p.: 218-220 °C. ^1H NMR ($CDCl_3$): δ 8.25 (2H, d, J=9.0 Hz), 7.77 (2H, d, J=9.0 Hz), 7.4 (2H, m), 7.2 (3H, m), 6.81 (1H, s), 6.55 (1H, s), 6.07 (1H, s), 6.02 (1H, s), 6.36 (1H, qa, J=1.1 Hz), 2.36 (3H, d, J=1.1 Hz).

Example 27

7-(2-Chloroacetyl)-8-methyl-5-(4-nitrophenyl)--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

To 45 cm^3 (564.6 mmoles) of chloroacetyl chloride, 15.0 g (46.4 mmoles) of 8-methyl--5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine are added under ice-water cooling in 10 minutes. After 5 minutes' stirring at 25 °C, the solution becomes cloudy. The mixture is stirred at 80 °C for 60 minutes, then boiled for 15 minutes. After cooling, the mixture is poured onto 450 g of ice, stirred for 3 hours, the crystals precipitated are filtered, washed three times using 60 cm^3 of water each time, and dried under a

lamp emitting infra red radiation. The crude product is boiled in 150 cm^3 of ethanol for 5 minutes. After cooling, the crystals are filtered, washed with ethanol and diethyl ether.

Thus, 15.5 g (83.5 %) of the title compound are obtained. M.p.: 228-229 °C.
Analysis: for $C_{19}H_{14}ClN_3O_5$ (399.79)
calculated: N 10.51 %;
found: N 10.28 %.
^1H NMR ($CDCl_3$): δ 8.28 (2H, d, J=8.8 Hz), 7.71 (2H, d, J=8.8 Hz), 6.77 (1H, s), 6.48 (1H, s), 6.38 (1H, bs), 6.05 (2H, s), 4.09 (2H, s), 2.28 (3H, s).

Example 28
7-(3-Chloropropionyl)-8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

To 45 cm^3 (461.9 mmoles) of 3-chloropropionyl chloride, 15.0 g (46.4 mmoles) of 8-methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine are added under ice-water cooling in 10 minutes. The mixture is stirred at 25 °C for 22 hours, then poured onto 450 g of ice. After 3 hours' stirring, the crystals precipitated are filtered, washed three times with 60 cm^3 of water each time, and dried under a lamp emitting infra red radiation. The crude product is dissolved in 300 cm^3 of dichloromethane, and washed

with 200 cm^3 of water. The organic phase is evaporated under reduced pressure, and the evaporation residue is boiled in 100 cm^3 of ethanol for 10 minutes. After cooling, the crystals are filtered, washed with ethanol and diethyl ether.

Thus, 14.1 g (73.4 %) of the title compound are obtained. M.p.: 207-209 °C.
Analysis: for $C_{20}H_{16}ClN_3O_5$ (413.82)
calculated: C 58.05 %, H 3.90 %, N 10.15 %, Cl 8.57 %;
found: C 58.66 %, H 4.02 %, N 9.96 %, Cl 8.53 %.
^1H NMR ($CDCl_3$): δ 8.28 (2H, d, J=8.8 Hz), 7.71 (2H, d, J=8.8 Hz), 6.77 (1H, s), 6.48 (1H, s), 6.35 (1H, bs), 6.05 (2H, bs), 3.86 (2H, m), 3.1-2.9 (2H, m), 2.27 (3H, s).

Example 29
8-Methyl-7-methylcarbamoyl-5-(4-nitrophenyl)--7H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine

5 g (11.3 mmoles) of the compound prepared according to Example 26, 50 cm^3 of ethanol and 14.4 cm^3 (136.6 mmoles) of 33 % methylamine in ethanol are transferred to an acid resistant steel bomb tube of 200 cm^3 capacity. The bomb tube is sealed, and the mixture is stirred at 90 °C for 8 hours. The mixture is allowed to stand at 25 °C for a night, on the other day the bomb tube is opened. The crystals precipitated are filtered, washed three times

using 5 cm^3 of ethanol each time, then twice with 20 cm^3 of diethyl ether each time.

Thus, 3.6 g (83.9 %) of the title compound are obtained. M.p.: higher than 250 °C. ^1H NMR ($CDCl_3$): δ 8.25 (2H, d, J=8.8 Hz), 7.67 (2H, d, J=8.8 Hz), 6.70 (1H, s), 6.40 (1H, s), 6.15 (1H, s), 6.10 (1H, m), 6.01 (2H, s), 2.97 (3H, d, J=4.8 Hz), 2.21 (3H, s).

Example 30

8-Methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine-7-carboxylic acid-(2-morpholino-4-ylethyl)amide

10.0 g (22.6 mmoles) of the compound prepared according to Example 26, 100 cm^3 of ethanol and 19.08 g (146.6 mmoles) of 4-(2-aminoethyl)morpholine are transferred to an acidresistant steel bomb tube of 200 cm^3 capacity. The bomb tube is sealed, and the mixture is stirred at 110 °C for 24 hours. On the next day, the bomb tube is opened, and the mixture is evaporated under reduced pressure. The evaporation residue is stirred in 400 cm^3 of water for 5 hours, then extracted three times using 200 cm^3 of chloroform each time. The organic phase is dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The 8.0 g of evaporation residue are transferred to a silica gel column that is eluted with a mixture of chloroform and

methanol. The adequate fraction is evaporated, the evaporation residue is stirred in 50 cm^3 of diisopropyl ether for an hour. The crystals are filtered, and washed with diisopropyl ether.

Thus, 5.8 g (35.8 %) of the title compound are obtained. M.p.: 218-220 °C.
^1H NMR (DMSÔ-d_6): δ 8.27 (2H, d, J=9.0 Hz), 7.88 (2H, d, J=9.0 Hz), 7.06 (1H, t, J=2.8 Hz), 6.98 (1H, s), 6.59 (1H, s), 6.31 (1H, s), 6.12 (2H, s), 3.60 (4H, m), 3.3 (2H, s), 2.5-2.1 (6H, m), 2.09 (3H, s).

Example 31
7-Guanidinocarbonyl-8-methyl-5-(4-nitrophenyl)--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

8.9 g (20 mmoles) of the compound prepared according to Example 26 are suspended in 300 cm^3 of absolute ethanol, and 4.0 g (40 mmoles) of 97 % guanidine hydrochloride are added. To the suspension, 2.3 g of sodium methylate are added in 15 minutes, and the mixture is boiled under stirring for 3 hours. After cooling, the suspension is filtered, and the filtrate is evaporated under reduced pressure. To the evaporation residue, 250 cm^3 of water are added, and, after an hour's stirring, the crystals obtained are filtered, and washed three times using 30 cm^3 of water each time. Thus, 7.6 g of crude product melting at 202-206 °C are obtained which is transferred to a

silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, the evaporation residue is crystallized in 40 cm^3 of diethyl ether. The crystals are filtered, and washed with diethyl ether.

Thus, 6.1 g (74.8 %) of the title compound are obtained. M.p.: 204-206 °C.
^1H NMR (DMSO-d_6): δ 8.21 (2H, d, J=9.0 Hz), 7.82 (2H, d, J=9.0 Hz), 7.00 (1H, s), 6.50 (1H, s), 6.31 (1H, s), 6.13 (1H, s), 6.05 (1H, s), 2.22 (3H, s).

Example 32
7-(4-Benzylpiperidine-1-ylcarbonyl)-8-methyl-5--(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

8.0 g (18 mmoles) of the compound prepared according to Example 26, 80 cm^3 of ethanol and 32 cm^3 (180 mmoles) of 4-benzylpiperidine are transferred to an acid-resistant steel bomb tube having 200 cm^3 capacity. The bomb tube is sealed, and the mixture is stirred at 110 °C for 24 hours. Then the bomb tube is opened, and the mixture is evaporated under reduced pressure. To the evaporation residue, 250 cm^3 of diethyl ether are added, and, after 2 hours' stirring, the crystals obtained are filtered and washed with diethyl ether.

Thus, 6.4 g (60.4 %) of the title compound are obtained. M.p.: 211-212.5 °C.

^{1}H NMR ($CDCl_3$): δ 8.20 (2H, d, J=8.8 Hz), 7.72 (2H, d, J=8.8 Hz), 7.40-7.00 (5H, m), 6.69 (1H, s), 6.46 (1H, s), 6.15 (1H, s), 6.03 (2H, s), 4.00 (2H, d, J=15 Hz), 2.66 (2H, t, J=13 Hz), 2.52 (2H, d, J=7 Hz), 2.07 (3H, s), 1.80-1.50 (3H, m), 1.3-1.1 (2H, m).

Example 33

7-[2-/N-Benzyl-(2-morpholinoethyl)amino/-acetyl]-8-methyl-5-(4-nitrophenyl)-7H--1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 12.0 g (30 mmoles) of the compound prepared according to Example 27, 250 cm^3 of acetonitrile and 14.9 g (66 mmoles) of benzyl-(2-morpholine-4-ylethyl)amine is boiled for 7 hours. After cooling, the reaction mixture is filtered, and the filtrate is evaporated under reduced pressure. The evaporation residue is dissolved in 300 cm^3 of dichloromethane, washed twice with 100 cm^3 of water each time, and the organic phase is evaporated under reduced pressure. The evaporation residue (11.4 g) is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure, then treated at a pressure of 0.1 mm Hg.

Thus, 10.0 g (57.1 %) of crystalline foam are obtained. M.p.: 69-70 °C.

Analysis: for $C_{32}H_{33}N_5O_6$ (583.65)

calculated: N 12.00 %;
found: N 11.82 %.
^{1}H NMR ($CDCl_3$): δ 8.23 (2H, d, J=8.8 Hz), 7.59 (2H, d, J=8.8 Hz), 7.25 (5H, m), 6.77 (1H, s), 6.44 (1H, s), 6.33 (1H, s), 6.04 (2H, s), 3.91 (3H, bs), 3.62 (5H, m), 2.93 (2H, m), 2.48 (2H, m), 2.37 (4H, m), 2.28 (3H, s).

Example 34

7-{2-[N-/2-(3,4-Dimethoxyphenyl)ethyl/-methylamino]acetyl}-8-methyl-5-(4-nitrophenyl)--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 14.4 g (36 mmoles) of the compound prepared according to Example 27, 200 cm^3 of acetonitrile and 15 g (76.8 mmoles) of N-/2-(3,4-dimethoxyphenyl)ethyl/methylamine is boiled for 5 hours. After cooling, the reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized in 200 cm^3 of water, the crystals are filtered, washed three times using 50 cm^3 of water each time, and dried under a lamp emitting infra red radiation. The crude product (19.7 g) is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure, and the evaporation residue (7.0 g) is dissolved in 20 cm^3 of ethyl acetate. To the solution obtained, a solution of 1.13 g (12.5 mmoles)

of anhydrous oxalic acid in 25 cm^3 of diethyl ether are added. After half an hour's stirring, the crystals precipitated are filtered, and washed with diethyl ether. Thus, 4.8 g of the monooxalate of the title compound are obtained, m.p. 124-125 °C. From the oxalate salt, the base is liberated with a 10 % aqueous sodium hydroxide solution, and extracted with dichloromethane, the organic phase is dried, and evaporated under reduced pressure. The evaporation residue is crystallized from a mixture of hexane and diethyl ether in a ratio of 1:1, and the crystals are filtered.

Thus, 1.6 g of the title compound are obtained. M.p.: 103-105 °C.

Analysis: for $C_{30}H_{30}N_4O_7$ (558.60)

calculated: N 10.03 %;

found: N 9.84 %.

^1H NMR ($CDCl_3$): δ 8.26 (2H, d, J=8.8 Hz), 7.70 (2H, d, J=8.8 Hz), 6.80-6.70 (4H, m), 6.45 (1H, s), 6.34 (1H, s), 6.05 (1H, s), 6.01 (1H, s), 3.85 (7H, bs), 3.5 (1H, bs), 2.80-2.50 (7H, m), 2.28 (3H, d, J=1.1 Hz).

Example 35

1-[2-/8-Methyl-5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-2-oxoethyl]pyrrolidine-2-one

To a solution of 2.85 g (33.5 mmoles) of 2-pyrrolidone in 60 cm^3 of dimethylsulfoxide, 3.75 g (33.4 mmoles) of potassium

tert.-butylate are added. The mixture is stirred for half an hour, then 10.95 g (27.4 mmoles) of the compound prepared according to Example 27 are added at 10 °C. The reaction mixture is stirred at 25 °C for an hour, then, 45 cm^3 of water are added to it, drop by drop, under cooling. The crystals precipitated are filtered, then transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The adequate fraction is evaporated under reduced pressure.

Thus, 3.47 g (28.3 %) of the title compound of yellow colour are obtained. M.p.: 235-237 °C.

^1H NMR ($CDCl_3$): δ 8.30 (2H, d, J=8.8 Hz), 7.70 (2H, d, J=8.8 Hz), 7.06 (1H, s), 6.63 (1H, s), 6.57 (1H, s), 6.13 (2H, bs), 4.6-4.1 (2H, m), 3.28 (2H, m), 2.26 (2H, m), 2.15 (3H, s), 1.96 (2H, m).

Example 36

7-/2-(4-Benzylpiperidinyl)acetyl/-8-methyl--5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

A mixture of 10.0 g (25 mmoles) of the compound prepared according to Example 27, 250 cm^3 of acetonitrile and 9.64 g (55 mmoles) of 4-benzyl-piperidine is boiled for 4 hours. The reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized from 250 cm^3 of water, stirred

at 25 °C for 3 hours, the crystals obtained are filtered, and washed with water. The crude product is suspended in 200 cm^3 of diethyl ether, and, after 30 minutes' stirring, filtered, and washed with diethyl ether.

Thus, 10.5 g (78.0 %) of the title compound are obtained. M.p.: 102-104 °C.
Analysis: for $C_{31}H_{30}N_4O_5$ (538.61)
calculated: C 69.13 %, H 5.61 %, N 10.40 %;
found: C 69.27 %, H 5.72 %, N 10.16 %.
^1H NMR ($CDCl_3$): δ 8.26 (2H, d, J=8.8 Hz), 7.68 (2H, d, J=8.8 Hz), 7.30-7.10 (5H, m), 6.75 (1H, s), 6.46 (1H, s), 6.32 (1H, s), 6.05 (2H, bs), 3.60-3.30 (2H, m), 3.00-2.85 (2H, m), 2.50 (2H, m), 2.26 (3H, s), 2.15 (2H, m), 1.6 (3H, m), 1.3 (2H, m).

Example 37

N-[2-/8-Methyl-5-(4-nitrophenyl)-7H-1,3--dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-2--oxoethyl]phthalimide

6.0 g (15.00 mmoles) of the compound prepared according to Example 27 are dissolved in 30 cm^3 of dimethylformamide. To the solution, 0.9 g (5.4 mmoles) of potassium iodide and 3.75 g (20.2 mmoles) of potassium phthalimide are added. The mixture is boiled for 2 hours, then, after cooling, 45 cm^3 of water are added to it, drop by drop. After an hour's stirring, the crystals obtained are filtered, and washed with water. The crude

product is recrystallized from ethanol.

Thus, 3.58 g (46.7 %) of the title compound are obtained. M.p.: 206-209 °C. ^{1}H NMR ($CDCl_3$): δ 8.28 (2H, d, J=8.8 Hz), 7.88 (2H, d, J=8.8 Hz), 7.74 (4H, m), 6.74 (1H, s), 6.53 (1H, s), 6.30 (1H, s), 6.05 (2H, bs), 4.82 (2H, m), 2.26 (3H, s).

Example 38

8-Methyl-7-[2-/4-(2-methoxyphenyl)-piperazinyl/acetyl]-5-(4-nitrophenyl)-7H--1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 12.0 g (30 mmoles) of the compound prepared according to Example 27, 150 cm^3 of acetonitrile and 12.8 g (66.6 mmoles) of 1-(2-methoxyphenyl)piperazine is boiled for 6 hours. After cooling, the reaction mixture is filtered, and the filtrate is evaporated under reduced pressure. The evaporation residue is crystallized from 150 cm^3 of water, stirred at 25 °C for half an hour, the crystals obtained are filtered, and washed with water. The 16.0 g (96 %) of crude product are transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The adequate fraction is evaporated under reduced pressure, the evaporation residue is crystallized from a mixture of petroleum ether (b.p.: 30-40 °C) and diethyl ether in a ratio of 2:1, and the crystals are filtered.

Thus, 10.1 g (60.6 %) of the title compound are obtained. M.p.: 119-120 °C.
^{1}H NMR ($CDCl_3$): δ 8.28 (2H, d, J=8.8 Hz), 7.88 (2H, d, J=8.8 Hz), 7.00-6.80 (4H, m), 6.78 (1H, s), 6.50 (1H, s), 6.35 (1H, bs), 6.04 (2H, bs), 3.85 (3H, s), 3.68 (1H, m), 3.48 (1H, m), 3.10 (4H, bs), 2.85 (2H, m), 2.75 (2H, m), 2.30 (3H, s).

Example 39

8-Methyl-7-[2-/4-(3-methoxyphenyl)-piperazinyl/acetyl]-5-(4-nitrophenyl)-7H--1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 4.36 g (10.9 mmoles) of the compound prepared according to Example 27, 70 cm^3 of acetonitrile and 4.2 g (21.8 mmoles) of 1-(3-methoxyphenyl)piperazine is boiled for 7 hours. After cooling, the reaction mixture is filtered, and the filtrate is evaporated under reduced pressure. The evaporation residue is crystallized from 30 cm^3 of water, stirred at 25 °C for half an hour, the crystals obtained are filtered, and washed with water. The 5.0 g of crude product are recrystallized from 100 cm^3 of ethyl alcohol, the crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 4.0 g (66.1 %) of the title compound are obtained. M.p.: 206-208 °C.
^{1}H NMR ($CDCl_3$): δ 8.28 (2H, d, J=8.8 Hz), 7.71 (2H, d, J=8.8 Hz), 7.15 (1H, t, J=8.2

Hz), 6.77 (1H, s), 6.55-6.35 (5H, m), 6.04 (2H, bs), 3.77 (3H, s), 3.60 (2H, m), 3.20 (4H, t, J=4.6 Hz), 2.80 (4H, m), 2.30 (3H, d, J=0.9 Hz).

Example 40

(±)-7-{2-[4-/2-Hydroxy-3-(2-methoxy-phenoxy)propyl/piperazinyl]acetyl}-8-methyl--5-(4-nitrophenyl)-7H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine

A mixture of 20 g (50 mmoles) of the compound prepared according to Example 27, 300 cm^3 of acetonitrile and 29.0 g (108.9 mmoles) of 1-(2-methoxyphenoxy)-3-piperazine--1-yl-2-propanol is boiled for 7 hours, then further 5.1 g (19.2 mmoles) of 1-(2-methoxy-phenoxy)-3-piperazine-1-yl-2-propanol are added to the mixture. The reaction mixture is boiled for further 24 hours, then cooled, and evaporated under reduced pressure. From the oily evaporation residue, twice 300 cm^3 of water are decanted, then the residue is dissolved in 450 cm^3 of dichloromethane, and the organic solution is washed twice using 300 cm^3 of water each time. The dichloromethane phase is dried, and evaporated under reduced pressure. The evaporation residue is crystallized from 200 cm^3 of water, stirred at 25 ^oC for 3 hours, the crystals obtained are filtered, and washed with water. The 19.2 g of crude product are transferred to a silica

gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, the evaporation residue is crystallized from diisopropyl ether, the crystals are filtered, and washed with diisopropyl ether.

Thus, 11.2 g (35.6 %) of the title compound are obtained. M.p.: 160-161.5 °C. Analysis: for $C_{33}H_{35}N_5O_8$ (629.68) calculated: C 62.95 %, H 5.60 %, N 11.12 %; found: C 63.52 %, H 5.55 %, N 11.08 %. ^{1}H NMR ($CDCl_3$): δ 8.28 (2H, d, J=8.8 Hz), 7.69 (2H, d, J=8.8 Hz), 7.00-6.85 (4H, m), 6.77 (1H, s), 6.49 (1H, s), 6.34 (1H, s), 6.05 (2H, m), 4.15 (1H, m), 4.01 (2H, d, J=5.2 Hz), 3.85 (3H, s), 3.65 (1H, m), 3.40 (1H, m), 2.70 (4H, m), 2.55 (6H, m), 2.23 (3H, d, J=1.0 Hz).

Example 41

8-Methyl-7-{3-[N-/2-(3,4-dimethoxyphenyl)-ethyl/methylamino]propionyl}-5-(4-nitro-phenyl)-7H-1,3-dioxolo-/4,5-h//2,3/-benzodiazepine

A mixture of 14.9 g (36 mmoles) of the compound prepared according to Example 28, 200 cm^3 of acetonitrile and 15.0 g (76.8 mmoles) of N-/2-(3,4-dimethoxyphenyl)ethyl/-methylamine is boiled for 3 hours. After cooling, the reaction mixture is filtered, the filtrate is evaporated under reduced

pressure. The evaporation residue is dissolved in 400 cm^3 of dichloromethane, and washed three times using 100 cm^3 of water each time. The organic phase is dried, and evaporated under reduced pressure. The evaporation residue (18.5 g) is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure, then treated at a pressure of 0.1 mm Hg, and the crystals are collected.

Thus, 15.3 g (74.3 %) of the title compound are obtained. M.p.: 64-66 °C.
Analysis: for $C_{31}H_{32}N_4O_7$ (572.62)
calculated: N 9.78 %;
found: N 9.48 %.
^1H NMR ($CDCl_3$): δ 8.24 (2H, d, J=8.7 Hz), 7.64 (2H, d, J=8.7 Hz), 6.80-6.70 (3H, m), 6.77 (1H, s), 6.48 (1H, s), 6.33 (1H, s), 6.04 (1H, s), 5.95 (1H, s), 3.85 (3H, s), 2.90-2.60 (8H, m), 2.37 (3H, s), 2.28 (3H, s).

Example 42

7-[3-/N-Benzyl-(2-morpholinoethyl)amino/-propionyl]-8-methyl-5-(4-nitrophenyl)-7H--1,3-dioxolo/4,5-h//2,3/- benzodiazepine

A mixture of 10.34 g (25 mmoles) of the compound prepared according to Example 28, 250 cm^3 of acetonitrile and 12.42 g (55.0 mmoles) of benzyl-(2-morpholine-4-ylethyl)amine

is boiled for 8 hours. The reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized from 150 cm^3 of water, stirred at 25 °C for 2 hours, the crystals obtained are filtered, and washed with water. The crude product (10.8 g) is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure, and treated at a pressure of 0.1 mm Hg. The crystals are collected.

Thus, 9.2 g (61.7 %) of the title compound are obtained. M.p.: 74-75 °C.
Analysis: for $C_{33}H_{35}N_5O_6$ (597.68)
calculated: C 66.32 %, H 5.90 %, N 11.72 %;
found: C 65.85 %, H 5.80 %, N 11.78 %.
^1H NMR ($CDCl_3$): δ 8.23 (2H, d, J=8.7 Hz), 7.59 (2H, d, J=8.7 Hz), 7.25 (5H, m), 6.75 (1H, s), 6.39 (1H, s), 6.33 (1H, s), 6.02 (2H, s), 3.65 (6H, m), 3.00-2.40 (12H, m), 2.28 (3H, d, J=1.2 Hz).

Example 43

8-Methyl-7-[3-/4-(2-methoxyphenyl)-piperazinyl/propionyl]-5-(4-nitrophenyl)--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 12.4 g (30 mmoles) of the compound prepared according to Example 28, 150 cm^3 of acetonitrile and 12.8 g (66.6 mmoles) of 1-(2-methoxyphenyl)piperazine is

boiled for 2.5 hours. After cooling, the reaction mixture is filtered, and the filtrate is evaporated under reduced pressure. The evaporation residue is crystallized from 150 cm^3 of water, stirred at 25 °C for 2 hours, the crystals obtained are filtered, and washed with water. The 17.0 g of crude product is heated to boiling in 120 cm^3 of water, and the latter is decanted from the oil. To the residue, 50 cm^3 of diisopropyl ether are added to crystallize the product. After an hour's stirring at 25 °C, the crystals obtained are filtered, and washed three times using 10 cm^3 of diisopropyl ether each time.

Thus, 15.4 g (90.2 %) of the title compound are obtained. M.p.: 171-173 °C.
Analysis: for $C_{31}H_{31}N_5O_6$ (569.62)
calculated: N 12.29 %;
found: N 12.39 %.
^1H NMR ($CDCl_3$): δ 8.27 (2H, d, J=8.7 Hz), 7.75 (2H, d, J=8.7 Hz), 7.00-6.80 (4H, m), 6.77 (1H, s), 6.50 (1H, s), 6.34 (1H, bs), 6.00 (2H, m), 3.86 (3H, s), 3.30-2.60 (12H, m), 2.28 (3H, s).

Example 44

8-Methyl-7-[3-/4-(3-methoxyphenyl)-piperazinyl/propionyl]-5-(4-nitrophenyl)--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

A mixture of 6.12 g (14.8 mmoles) of the compound prepared according to Example

28, 100 cm^3 of acetonitrile and 5.5 g (28.6 mmoles) of 1-(3-methoxyphenyl)piperazine is boiled for 7 hours. The reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized from 150 cm^3 of water, stirred at 25 °C for an hour, the crystals obtained are filtered, and washed with water. The 8.0 g of crude product are transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure. The evaporation residue is crystallized from 85 cm^3 of diethyl ether. After an hour's stirring at 25 °C, the crystals obtained are filtered, and washed three times using 10 cm^3 of diethyl ether each time.

Thus, 5.06 g (60.1 %) of the title compound are obtained. M.p.: 165-166 °C.
^{1}H NMR (DMSO-d_6): δ 8.33 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.8 Hz), 7.10 (2H, m), 6.68 (1H, s), 6.54 (1H, s), 6.506.30 (3H, m), 6.15 (1H, s), 6.10 (1H, s), 3.71 (3H, s), 3.40-2.60 (12H, m), 2.17 (3H, s).

Example 45

7-[3-/4-(4-Fluorophenyl)-4-hydroxy-piperidinyl/propionyl]-8-methyl-5--(4-nitrophenyl)-7H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine

A mixture of 12.4 g (30 mmoles) of the compound prepared according to Example 28,

250 cm^3 of acetonitrile and 12.9 g (66.1 mmoles) of 4-(4-fluorophenyl)piperidine-4-ol is boiled for 2 hours. After cooling, the reaction mixture is evaporated under reduced pressure. The evaporation residue is crystallized from 300 cm^3 of water, stirred at 25 °C for 2 hours, the crystals obtained are filtered, and washed with water. The 17.0 g of crude product are suspended in 100 cm^3 of diisopropyl ether, and, after an hour's stirring at 25 °C, the crystals are filtered, and washed three times using 20 cm^3 of diisopropyl ether each time.

Thus, 16.5 g (96.1 %) of the title compound are obtained. M.p.: 134-136 °C.
Analysis: for $C_{31}H_{29}FN_4O_6$ (572.60)
calculated: N 9.78 %;
found: N 9.88 %.
^1H NMR (DMSO-d_6): δ 8.33 (2H, d, J=8.8 Hz), 7.77 (2H, d, J=8.8 Hz), 7.46 (2H, m), 7.07 (3H, m), 6.61 (1H, s), 6.51 (1H, s), 6.15 (1H, s), 6.10 (1H, s), 4.90 (1H, s), 3.40-2.40 (13H, m), 2.18 (3H, s), 1.90 (2H, m), 1.60 (2H, m).

Example 46

5-(4-Aminophenyl)-8-methyl-7H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine-7-carboxylic acid-(2-morpholino-4-ylethyl)amide

2.0 g (4.17 mmoles) of the compound prepared according to Example 30 are

transferred into a mixture of 80 cm^3 of ethanol and 20 cm^3 of water. To the mixture, 0.4 g of 10 % palladium/carbon catalyst, then, in 4 minutes, 4.0 cm^3 (80.6 mmoles) of 98 % hydrazine hydrate are added at 15 to 20 ^oC. The mixture is stirred at 25 ^oC for 4.5 hours, the catalyst is filtered, and washed with ethanol. The filtrate is evaporated under reduced pressure, and, to the residue, 120 cm^3 of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, and the evaporation residue is crystallized from diethyl ether. The crystals obtained are filtered, and washed with diethyl ether.

Thus, 0.52 g (27.8 %) of the title compound are obtained. M.p.: 249-251 ^oC.
Analysis: for $C_{24}H_{27}N_5O_4$ (449.51)
calculated: C 64.13 %, H 6.05 %, N 15.58 %;
found: C 64.36 %, H 6.20 %, N 15.20 %.
^1H NMR ($CDCl_3$): δ 7.36 (2H, d, J=8.3 Hz), 6.79 (1H, m), 6.67 (2H, s), 6.65 (2H, d, J=8.3 Hz), 6.13 (1H, s), 6.01 (1H, s), 5.95 (1H, s), 4.01 (2H, bs), 3.80 (4H, t, J=4.5 Hz), 3.5-3.3 (2H, m), 2.65-2.4 (6H, m), 2.23 (3H, s).

Example 47

5-(4-Aminophenyl)-7-(guanidinocarbonyl)-8--methyl-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine monohydrate

3.0 g (7.34 mmoles) of the compound prepared according to Example 31 are transferred into a mixture of 150 cm^3 of methanol and 30 cm^3 of water. To the mixture, 0.9 g of 10 % palladium/carbon catalyst are added, then, in 15 minutes, 6.0 cm^3 (120 mmoles) og 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 2.5 hours. Then, the catalyst is filtered, and washed with methanol. The filtrate is evaporated under reduced pressure, and, to the residue, 100 cm^3 of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, and the evaporation residue is crystallized from diethyl ether. The crystals obtained are filtered, and washed with diethyl ether.

Thus, 1.54 g (55.6 %) of the title compound are obtained. M.p.: 216-218 °C.
^{1}H NMR (DMSO-d_6): δ 7.19 (2H, d, J=8.4 Hz), 7.1-6.65 (2H, br), 6.92 (1H, s), 6.64 (1H, s), 6.54 (2H, d, J=8.4 Hz), 6.22 (1H, s), 6.11 (1H, s), 6.04 (1H, s), 5.55 (2H, s),

3.32 (2H, s), 2.19 (3H, s).

Example 48

5-(4-Aminophenyl)-7-/(4-benzylpiperidine-1--yl)carbonyl/-8-methyl-7H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine

5.0 g (9.5 mmoles) of the compound prepared according to Example 32 are dissolved in a mixture of 200 cm^3 of chloroform and 90 cm^3 of methanol. To the solution obtained, 5.0 g of 10 % palladium/carbon catalyst suspended in 10 cm^3 of methanol are added, and the mixture is vigorously stirred under hydrogen atmosphere at room temperature. The reduction is finished in 16 hours. The catalyst is filtered, washed three times using 50 cm^3 of methanol each time, and the filtrate is evaporated under reduced pressure. The evaporation residue is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated under reduced pressure. To the residue, 20 cm^3 of diethyl ether are added, and the mixture is stirred for an hour. The crystals obtained are filtered, washed three times using 10 cm^3 of diethyl ether each time, and dried under a lamp emitting infra red radiation.

Thus, 1.4 g (32.6 %) of the title compound are obtained. M.p.: 179-181 ^oC.

Analysis: for $C_{30}H_{30}N_4O_3$ (494.60):

calculated: N 11.33 %;
found: N 11.06 %.
^{1}H NMR ($CDCl_3$): δ 7.67 (1H, s), 7.4-7.2 (4H, m), 7.2-7.05 (4H, m), 6.87 (1H, s), 6.80 (1H, d, J=2.4 Hz), 6.78 (1H, d, J=2.4 Hz), 6.08 (2H, s), 4.20 (2H, br), 4.10 (2H, m), 2.72 (3H, s), 2.70-2.55 (1H, m), 2.50-2.45 (1H, m), 2.43 (2H, d, J=7.2 Hz), 1.6 (1H, m), 1.5 (1H, m), 1.4 (1H, m), 1.1-0.95 (1H, m), 0.85-0.70 (1H, m).

Example 49

5-(4-Aminophenyl)-8-methyl-7-/2-(2-morpholino-ethylamino)acetyl/-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine monohydrate

6.0 g (10.3 mmoles) of the compound prepared according to Example 33 are transferred into a mixture of 240 cm^3 of methanol and 50 cm^3 of water. To the mixture, 4.8 g of 10 % palladium/carbon catalyst, then, in 20 minutes, 24.0 cm^3 (484 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 ^oC. The mixture is stirred at 25 ^oC for 100 hours, then further 2.4 g of 10 % palladium/carbon catalyst and 12.0 cm^3 (242 mmoles) of 98 % hydrazine hydrate are added. After further 72 hours' stirring, the catalyst is filtered, washed with methanol, and the filtrate is evaporated under reduced pressure. To the residue, 100 cm^3 of water and 150 cm^3 of dichloromethane are added. After 5 minutes'

stirring, the phases are separated, the aqueous phase is still extracted twice with 150 cm^3 of dichloromethane each time. The organic phase is dried, and evaporated under reduced pressure. The evaporation residue is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 3.65 g (76.7 %) of the title compound are obtained. M.p.: 92-94 °C.
Analysis: for $C_{25}H_{29}N_5O_4.H_2O$ (481.56)
calculated: N 14.54 %;
found: N 14.25 %.
^1H NMR (DMSO-d_6): δ 7.18 (2H, d, J=8.4 Hz), 7.00 (1H, s), 6.72 (1H, s), 6.58 (2H, d, J=8.4 Hz), 6.48 (1H, s), 6.15 (1H, s), 6.08 (1H, s), 5.75 (2H, bs), 3.73 (1H, d, J=16.9 Hz), 3.54 (4H, t, J=4.6 Hz), 3.30 (1H, d, J=16.9 Hz), 3.05 (1H, m), 2.62 (2H, t, J=6.0 Hz), 2.40-2.25 (6H, m), 2.16 (3H, s).

Example 50

5-(4-Aminophenyl)-7-{2-[N-/2-(3,4-dimethoxyphenyl)ethyl/methylamino]acetyl}-8-methyl--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

7.0 g (12.5 mmoles) of the compound prepared according to Example 34 are added

to a mixture of 400 cm^3 of ethanol and 84 cm^3 of water. To the mixture, 2.8 g of 10 % palladium/carbon catalyst, and, in 30 minutes, 17.5 cm^3 (353 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 73 hours. Then, the catalyst is filtered, washed with ethanol, and the filtrate is evaporated under reduced pressure. To the residue, 80 cm^3 of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is suspended in diisopropyl ether, then filtered, and washed with diisopropyl ether.

Thus, 3.95 g (59.8 %) of the title compound are obtained. M.p.: 88-90 °C.
Analysis: for $C_{30}H_{32}N_4O_5$ (528.59)
calculated: N 10.60 %;
found: N 10.32 %.
^1H NMR ($CDCl_3$): δ 7.32 (2H, d, J=8.6 Hz), 6.80-6.67 (5H, m), 6.65 (2H, d, J=8.6 Hz), 6.31 (1H, s), 6.03 (1H, s), 5.96 (1H, s), 3.98 (2H, bs), 3.83 (6H, s), 3.79 (1H, d, J=16.2 Hz), 3.41 (1H, d, J=16.2 Hz), 2.85-2.65 (4H, m), 2.46 (3H, s), 2.28 (3H, s).

Example 51

5-(4-Aminophenyl)-8-methyl-7-[2-/4-(2--methoxyphenyl)piperazinyl/acetyl]-7H-1,3--dioxolo/4,5-h//2,3/benzodiazepine

5.5 g (9.9 mmoles) of the compound

prepared according to Example 38 are added to a mixture of 220 cm^3 of ethanol and 55 cm^3 of water. To the mixture, 1.65 g 10 % palladium/carbon catalyst, and, in 10 minutes, 9.0 cm^3 (182 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 2 hours. Then, the catalyst is filtered, washed with ethanol, and the filtrate is evaporated under reduced pressure. To the residue, 170 cm^3 of water are added. After 2 hours' stirring, the crystals are filtered, and washed with water. The crude product is suspended in diisopropyl ether, then filtered, and washed with diisopropyl ether.

Thus, 4.3 g (81.4 %) of the title compound are obtained. M.p.: 130-132 °C.
^{1}H NMR ($CDCl_3$): δ 7.33 (2H, d, J=8.7 Hz), 7.0-6.8 (4H, m), 6.74 (1H, s), 6.73 (1H, s), 6.66 (2H, d, J=8.7 Hz), 6.32 (1H, d, J=1.4 Hz), 6.04 (1H, d, J=1.3 Hz), 5.99 (1H, d, J=1.3 Hz), 4.03 (2H, bs), 3.84 (3H, s), 3.68 (1H, d, J=15.6 Hz), 3.39 (1H, d, J=15.6 Hz), 3.1 (4H, bs), 2.902.65 (4H, m), 2.30 (3H, d, J=1.1 Hz).

Example 52

(±)-5-(4-Aminophenyl)-7-{2-[4-/2-hydroxy--3-(2-methoxyphenoxy)propyl/piperazinyl]-acetyl}-8-methyl-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

6.3 g (10 mmoles) of the compound prepared according to Example 15 are added to a mixture of 180 cm^3 of ethanol and 36 cm^3 of water. To the mixture, 2.5 g of 10 % palladium/carbon catalyst, and, in 15 minutes, 12.0 cm^3 (242 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 4 hours, then the catalyst is filtered, washed with ethanol, and the filtrate is evaporated under reduced pressure. To the residue, 200 cm^3 of water are added. After 2 hours' stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, and the evaporation residue is crystallized from diethyl ether. The crystals obtained are filtered, and washed with diethyl ether.

Thus, 3.4 g (56.8 %) of the title compound are obtained. M.p.: 118-120 °C.
^{1}H NMR ($CDCl_3$): δ 7.30 (2H, d, J=8.7 Hz), 7.00-6.80 (4H, m), 6.72 (1H, s), 6.71 (1H, s), 6.64 (2H, d, J=8.7 Hz), 6.3 (1H, d, J=1.1 Hz), 6.02 (1H, s), 5.97 (1H, s), 4.09 (1H, m), 4.01 (4H, m), 3.83 (3H, s), 3.63 (1H, dd, J=15.7 and 2.7 Hz), 3.33 (1H, dd, J=15.7 Hz and 2.6 Hz), 2.67 (4H, m), 2.62-2.42 (7H, m), 2.28 (3H, d, J=1.1 Hz).

Example 53

5-(4-Aminophenyl)-7-[3-/2-(3,4-dimethoxyphenyl)-N-methylethylamino/propionyl]-8--methyl-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine dihydrate

3.0 g (5.2 mmoles) of the compound prepared according to Example 41 are added to a mixture of 100 cm^3 of methanol and 20 cm^3 of water. To the mixture, 2.4 g of 10 % palladium/carbon catalyst, and, in 30 minutes, 12.0 cm^3 (242 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 22.5 hours. Then, the catalyst is filtered, washed with methanol, and the filtrate is evaporated under reduced pressure. To the residue, 50 cm^3 of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The adequate fraction is evaporated, the evaporation residue is treated at a pressure of 0.1 mm Hg, and the crystals are collected.

Thus, 1.6 g (57.1 %) of the title compound are obtained. M.p.: 71-72.5 °C.

^{1}H NMR (DMSO-d_6): δ 7.19 (2H, d, J=8.6 Hz), 6.98 (1H, s), 6.76 (2H, m), 6.65 (1H, m), 6.68 (1H, s), 6.57 (2H, d, J=8.6 Hz), 6.45 (1H, s), 6.13 (1H, s), 6.05 (1H, s), 5.74 (2H, bs), 3.70 (3H, s), 3.69 (3H, s), 2.65-2.40

(8H, m), 2.20 (3H, s), 2.13 (3H, d, J=1.0 Hz).

Example 54

5-(4-Aminophenyl)-7-[3-/N-benzyl-(2--morpholinoethylamino)/propionyl]-8-methyl--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

5.2 g (8.7 mmoles) of the compound prepared according to Example 42 are added to a mixture of 175 cm^3 of methanol and 35 cm^3 of water. To the mixture, 1.4 g of 10 palladium/carbon catalyst, and, in 10 minutes, 7.0 cm^3 (141 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 24 hours. Then, the catalyst is filtered, washed with methanol, and the filtrate is evaporated under reduced pressure. To the residue, 100 cm^3 of water and 150 cm^3 of dichloromethane are added. After 5 minutes' stirring, the phases are separated, and the aqueous phase is still twice extracted with 150 cm^3 of dichloromethane each time. The organic phase is dried, evaporated under reduced pressure, and the evaporation residue is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The appropriate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 0.4 g (8.2 %) of the title compound are obtained (thin-layer chromatography: using a mixture of ethanol and ammonia in a ratio of 9:1, R_f = 0.75).
M.p.: 114-116 °C.
^{1}H NMR ($CDCl_3$): δ 7.31 (2H, d, J=8.7 Hz), 7.26 (5H, m), 6.72 (1H, s), 6.64 (2H, d, J=8.7 Hz), 6.62 (1H, s), 6.31 (1H, d, J=1.6 Hz), 6.05 (1H, d, J=1.6 Hz), 5.97 (1H, d, J=1.6 Hz), 3.98 (2H, s), 3.64 (6H, m), 2.93-2.68 (4H, m), 2.63 (2H, m), 2.44 (2H, m), 2.36 (4H, m), 2.25 (3H, s).

Example 55

5-(4-Aminophenyl)-8-methyl-7-/3-(2-morpholino-ethylamino)propionyl/-7H-1,3-dioxolo/4,5-h/-/2,3/benzodiazepine

When the compound prepared according to Example 42 is reduced by the method of Example 54, the debenzyl derivative of the compound according to Example 54 is also formed in the reaction. The two compounds are separated by the above column chromatographic method. The appropriate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 0.7 g (16.9 %) of the title compound are obtained (thin-layer chromatography: using a mixture of ethanol and ammonia in a ratio

of 9:1, R_f = 0.65).
M.p.: 122-124 °C.
Analysis: for $C_{26}H_{31}N_5O_4$ (477.57)
calculated: N 14.66 %;
found: N 14.46 %.
^1H NMR ($CDCl_3$): δ 7.32 (2H, d, J=8.6 Hz), 6.67 (2H, s), 6.64 (2H, d, J=8.6 Hz), 6.32 (1H, d, J=1.1 Hz), 6.04 (1H, d, J=1.1 Hz), 5.97 (1H, d, J=1.1 Hz), 4.10 (2H, bs), 3.68 (4H, t, J=4.7 Hz), 3.2-2.5 (8H, m), 2.43 (4H, t, J=4.6 Hz), 2.27 (3H, d, J=1.1 Hz).

Example 56

5-(4-Aminophenyl)-8-methyl-7-[3-/4-(2--methoxyphenyl)piperazinyl/propionyl]-7H--1,3-dioxolo/4,5-h//2,3/benzodiazepine

10.2 g (17.9 mmoles) of the compound prepared according to Example 43 are added to a mixture of 300 cm^3 of ethanol and 60 cm^3 of water. To the mixture, 4.0 g of 10 % palladium/carbon catalyst, and, in 20 minutes, 20 cm^3 (404 mmoles) of 98 % hydrazine hydrate are added at 20-25 °C. The mixture is stirred at 25 °C for 24 hours. Then, the catalyst is filtered, and washed with ethanol. The filtrate is evaporated under reduced pressure. To the residue, 200 cm^3 of water are added. After an hour's stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of

chloroform and methanol. The appropriate fraction is evaporated, the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 1.15 g (11.9 %) of the title compound are obtained. M.p.: 190-194 °C. ^{1}H NMR ($CDCl_3$): δ 7.35 (2H, d, J(8.7 Hz). 7.1-6.8 (4H, m), 6.74 (1H, s), 6.73 (1H, s), 6.64 (2H, d, J=8,7 Hz), 6.32 (1H, d, J=1.2 Hz), 6.02 (1H, d, J=1.1 Hz), 5.93 (1H, d, J=1.1 Hz), 4.00 (2H, bs), 3.85 (3H, s), 3.07 (4H, m), 3.0-2.7 (4H, m), 2.69 (4H, m), 2.28 (3H, d, J=1.1 Hz).

Example 57

5-(4-Aminophenyl)-8-methyl-7-[3-/4-(3--methoxyphenyl)piperazinyl/propionyl]-7H--1,3-dioxolo/4,5-h//2,3/benzodiazepine

5.0 g (8.8 mmoles) of the compound prepared according to Example 44 are added to a mixture of 250 cm^3 of ethanol and 50 cm^3 of water. To the mixture, 1.5 g of 10 % palladium/carbon catalyst, and, in 10 minutes, 8 cm^3 (160 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 5 hours, then, the catalyst is filtered, washed with ethanol, and the filtrate is evaporated under reduced pressure. To the residue, 100 cm^3 of water are added. After an hour's stirring, the

crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The appropriate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 2.9 g (61.2 %) of the title compound are obtained. M.p.: 105-106.5 °C.
Analysis: for $C_{31}H_{33}N_5O_4.H_2O$ (557.66)
calculated: C 66.76 %, H 6.33 %, N 12.56 %;
found: C 66.57 %, H 6.24 %, N 12.54 %.
^1H NMR ($CDCl_3$): δ 7.34 (2H, d, J=8.5 Hz), 7.14 (1H, t, J=8.1 Hz), 6.72 (1H, s), 6.71 (1H, s), 6.62 (2H, d, J=8.5 Hz), 6.51 (1H, dd, J=8.3 and 2.3 Hz), 6.44 (1H, t, J=2,3 Hz), 6.40 (1H, dd, J=8.0 and 2.3 Hz), 6.31 (1H, d, J=0.8 Hz), 6.00 (1H, d, J=1.2 Hz), 5.92 (1H, d, J=1.2 Hz), 4.04 (2H, s), 3.77 (3H, s), 3.14 (4H, t, J=4.8 Hz), 3.0-2.7 (4H, m), 2.61 (4H, t, J=4.8 Hz), 2.27 (3H, d, J=1.2 Hz).

Example 58

5-(4-Aminophenyl)-7-[3-/4-(4-fluorophenyl)--4-hydroxypiperidine-1-yl/propionyl]-8-methyl-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

9.0 g (15.7 mmoles) of the compound prepared according to Example 45 are added to a mixture of 360 cm^3 of ethanol and 70

cm^3 of water. To the mixture, 3.6 g of 10 % palladium/carbon catalyst, and, in 20 minutes, 18 cm^3 (363 mmoles) of 98 % hydrazine hydrate are added at 20 to 25 °C. The mixture is stirred at 25 °C for 68 hours. Then, the catalyst is filtered, washed with ethanol, and the filtrate is evaporated under reduced pressure. To the residue, 200 cm^3 of water are added. After 2 hours' stirring, the crystals are filtered, and washed with water. The crude product is transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The appropriate fraction is evaporated, and the evaporation residue is crystallized from diisopropyl ether. The crystals obtained are filtered, and washed with diisopropyl ether.

Thus, 3.47 g (40.87 %) of the title compound are obtained. M.p.: 130-132 °C. Analysis: for $C_{31}H_{31}FN_4O_4$ (542.62) calculated: C 68.62 %, H 5.76 %, N 10.33 %; found: C 68.52 %, H 5.88 %, N 10.12 %. ^1H NMR (DMSO-d_6): δ 7.47 (2H, m), 7.21 (2H, d, J=8.6 Hz), 7.10 (2H, m), 6.99 (1H, s), 6.72 (1H, s), 6.59 (2H, d, J=8.6 Hz), 6.46 (1H, s), 6.14 (1H, s), 6.05 (1H, s), 5.71 (2H, s), 4.82 (1H, s), 2.67 (6H, m), 2.43 (2H, m), 2.16 (3H, s), 1.85 (2H, m), 1.57 (2H, m).

Example 59

5-(4-Aminophenyl)-7-(2-chloroacetyl)-8-methyl--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

4.0 g (10 mmoles) of the compound prepared according to Example 27 are transferred into 160 cm^3 of ethanol, 9.0 g (40 mmoles) of crystalline tin(II) chloride ($SnCl_2.2H_2O$) are added, and the mixture is boiled for 1.5 hours. After cooling, the reaction mixture is evaporated. To the residue, 120 cm^3 of water are added, and the mixture is extracted three times using 100 cm^3 of dichloromethane each time. The combined dichloromethane layers are washed twice with 30 cm^3 of 5 % aqueous sodium hydroxide solution each time, and twice with 150 cm^3 of water each time, then dried, and evaporated under reduced pressure. To the evaporation residue, 50 cm^3 of diisopropyl ether are added. After 30 minutes' stirring, the crystals are filtered.

Thus, 1.9 g (51.6 %) of the title compound are obtained. M.p.: 197-199 °C.

^1H NMR ($CDCl_3$ + DMSO-d_6): δ 7.27 (2H, d, J=8.6 Hz), 6.75 (1H, s), 6.72 (1H, s), 6.65 (2H, d, J=8.6 Hz), 6.35 (1H, s), 6.02 (2H, bs), 4.59 (2H, bs), 4.35 (2H, m), 2.25 (3H, d, J=1.0 Hz).

Example 60

5-(4-Aminophenyl)-7-(3-chloropropionyl)-8--methyl-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine

6.18 g (15 mmoles) of the compound prepared according to Example 28 are transferred into 180 cm^3 of ethanol, 16.92 g (75 mmoles) of crystalline tin(II) chloride ($SnCl_2.2H_2O$) are added, and the mixture is boiled for 70 minutes. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 200 cm^3 of water are added, and the pH of the solution is adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted five times using 200 cm^3 of dichloromethane each time. The combined dichloromethane layers are washed twice with 250 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. To the evaporation residue, 100 cm^3 of diisopropyl ether are added. After 60 minutes' stirring, the crystals are filtered, and washed with diisopropyl ether. The crude product is recrystallized from ethanol.

Thus, 1.75 g (30.7 %) of the title compound are obtained. M.p.: 162-165 °C.
Analysis: for $C_{20}H_{18}ClN_3O_3$ (383.84)
calculated: N 10.95 %;
found: N 10.65 %.

^{1}H NMR ($CDCl_3$): δ 7.33 (2H, d, J=8.7 Hz), 6.73 (2H, s), 6.66 (2H, d, J=8.7 Hz), 6.33 (1H, d, J=1.3 Hz), 6.05 (1H, d, J=1.3 Hz), 5.98 (1H, d, J=1.3 Hz), 4.02 (2H, bs), 3.85 (1H, m), 3.75 (1H, m), 2.90 (1H, m), 2.27 (3H, d, J=1.3 Hz).

Example 61

5-(4-Aminophenyl)-8-methyl-7-methylcarbamoyl--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine

4.0 g (10.5 mmoles) of the compound prepared according to Example 29 are transferred into 200 cm^3 of ethanol, 10.64 g (47.2 mmoles) of crystalline tin(II) chloride ($SnCl_2.2H_2O$) are added, and the mixture is boiled for 2 hours. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 150 cm^3 of water are added, and the pH of the solution is adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted three times using 300 cm^3 of dichloromethane each time. The combined dichloromethane layers are dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. To the evaporation residue, 30 cm^3 of diisopropyl ether are added. After 60 minutes' stirring, the crystals are filtered, and washed with diisopropyl ether.

Thus, 1.02 g (27.7 %) of the title compound are obtained. M.p.: 188-190 °C.

^{1}H NMR ($CDCl_3$): δ 7.27 (2H, d, J=8.6 Hz), 6.66 (1H, s), 6.65 (1H, s), 6.62 (2H, d, J=8.6 Hz), 6.13 (1H, d, J=1.0 Hz), 6.05 (1H, m), 6.00 (1H, s), 5.94 (1H, s), 3.7 (2H, bs), 2.92 (3H, d, J=5.0 Hz), 2.22 (3H, d, J=1.2 Hz).

Example 62

1-[2-/5-(4-Aminophenyl)-8-methyl-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-2-oxoethyl]pyrrolidine-2-one monohydrate

2.56 g (5.7 mmoles) of the compound prepared according to Example 35 are transferred into 100 cm^3 of methanol, 6.4 g (28.4 mmoles) of crystalline tin(II) chloride ($SnCl_2.2H_2O$) are added, and the mixture is boiled for 2 hours. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 100 cm^3 of water are added, and the pH of the solution is adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted three times using 300 cm^3 of dichloromethane each time. The combined dichloromethane phases are washed with 250 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. To the evaporation residue, 30 cm^3 of diethyl ether are added. After 60 minutes' stirring, the crystals are filtered, and washed with diethyl ether.

Thus, 2.14 g (85.9 %) of the title compound are obtained. M.p.: 103-105 °C. ^{1}H NMR ($CDCl_3$): δ 7.33 (2H, d, J=8.6 Hz), 6.73 (1H, s), 6.71 (1H, s), 6.63 (2H, d, J=8.6 Hz), 6.28 (1H, d, J=1.2 Hz), 6.04 (1H, bs), 5.98 (1H, bs), 4.57 (1H, d, J=17.0 Hz), 4.19 (1H, d, J=17.0 Hz), 3.99 (2H, bs), 3.49 (2H, t, J=7.2 Hz), 2.42 (2H, t, J=8.1 Hz), 2.26 (3H, s), 2.04 (2H, m).

Example 63

N-[2-/5-(4-Aminophenyl)-8-methyl-7H-1,3--dioxolo/4,5-h//2,3/benzodiazepine-7-yl/-2--oxoethyl]phthalimide

4.02 g (7.9 mmoles) of the compound prepared according to Example 37 are transferred into 400 cm^3 of methanol, 8.9 g (39.4 mmoles) of crystalline tin(II) chloride ($SnCl_2.2H_2O$) are added, and the mixture is boiled for 72 hours. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 200 cm^3 of water are added, and the pH of the solution is adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted three times using 300 cm^3 of dichloromethane each time. The combined dichloromethane layers are washed twice using 250 cm^3 of water each time, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. To the evaporation

residue, 30 cm^3 of diethyl ether are added. After 60 minutes' stirring, the crystals are filtered, and washed with diethyl ether. The crude product is transferred to a silica gel column that is eluted with a mixture of hexane and acetone. The appropriate fraction is evaporated, and the residue is stirred in 30 cm^3 of diethyl ether for half an hour. The crystals obtained are filtered.

Thus, 1.52 g (40.2 %) of the title compound are obtained. M.p.: 189-191 °C. ^1H NMR ($CDCl_3$): δ 7.85 (2H, m), 7.70 (2H, m), 7.36 (2H, d, J=8.6 Hz), 6.77 (1H, s), 6.70 (1H, s), 6.66 (2H, d, J=8.6 Hz), 6.27 (1H, s), 6.04 (1H, s), 6.00 (1H, s), 5.06 (1H, d, J=16.1 Hz), 4.51 (1H, d, J=16.1 Hz), 3.9 (2H, br), 2.25 (3H, d, J=0.8 Hz).

Example 64

5-(4-Aminophenyl)-8-methyl-7-[2-/4-(3--methoxyphenyl)piperazinyl/acetyl]-7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine dihydrate

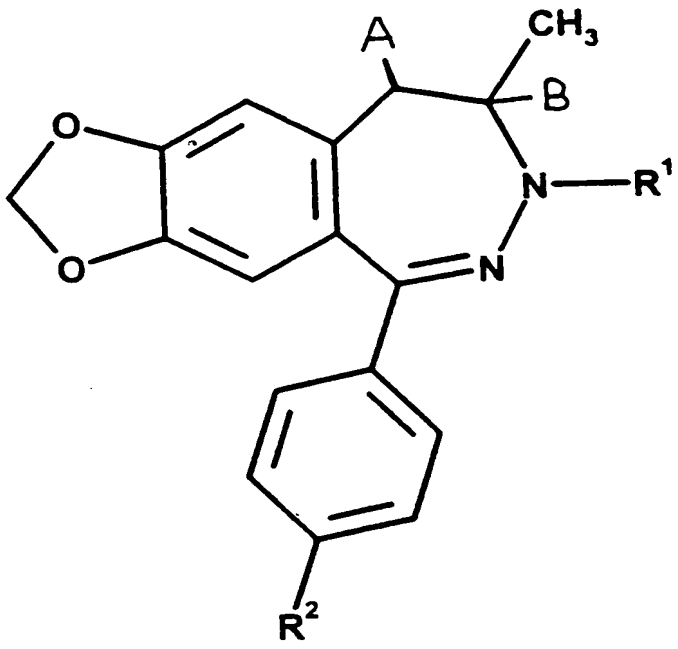
4.0 g (7.2 mmoles) of the compound prepared according to Example 39 are transferred into 100 cm^3 of ethanol, 8.11 g (36 mmoles) of crystalline tin(II) chloride ($SnCl_2.2H_2O$) are added, and the mixture is boiled for 7.5 hours. After cooling, the reaction mixture is evaporated under reduced pressure. To the residue, 100 cm^3 of water are added, and the pH of the solution is

adjusted to 11 by the addition of 10 % aqueous sodium hydroxide solution. The mixture is extracted three times using 300 cm^3 of dichloromethane each time. The combined dichloromethane layers are dried, and evaporated under reduced pressure. To the evaporation residue, 30 cm^3 of diethyl ether are added. After 30 minutes' stirring, the crystals are filtered. The crude product is transferred to a silica gel column that is eluted with a mixture of chloroform and methanol. The appropriate fraction is evaporated, and the residue is stirred in 30 cm^3 of diethyl ether. The crystals obtained are filtered.

Thus, 0.25 g (6.6 %) of the title compound are obtained. M.p.: 148-150 °C.
Analysis: for $C_{30}H_{31}N_5O_4.2H_2O$ (561.64)
calculated: C 64.16 %, H 6.28 %, N 12.47 %;
found: C 64.66 %, H 6.56 %, N 12.33 %.
^1H NMR ($CDCl_3$): δ 7.32 (2H, d, J=8.7 Hz), 7.14 (1H, t, J=8.1 Hz), 6.73 (2H, s), 6.66 (2H, d, J=8.7 Hz), 6.51 (1H, dd, J=8.0 and 1.8 Hz), 6.42 (2H, m), 6.33 (1H, d, J=1.1 Hz), 6.03 (1H, s), 5.99 (1H, s), 3.99 (2H, bs), 3.78 (3H, s), 3.69 (1H, d, J=15.6 Hz), 3.37 (1H, d, J=15.6 Hz), 3.20 (4H, t, J=5.0 Hz), 2.74 (4H, m), 2.29 (3H, d, J=1.1 Hz).

Claims:

1. A 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I



I

wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a C_{3-6} cycloalkyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two C_{1-4} alkyl group(s), a C_{1-4} alkyl group which latter is

optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 substituent(s), wherein the substituent consists of a C_{1-4} alkoxy group, or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 substituents, wherein the substituent is a C_{1-4} alkoxy group,

n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2, or

A forms together with B a valence bond between the carbon atoms in positions 8 and 9, and in this case

R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group, a C_{3-6} cycloalkyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C_{1-4} alkoxy group, or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 3 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is

optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a halo atom or a C_{1-4} alkoxy group, and, in case of the phenoxy(C_{1-4} alkyl) group, the alkyl group is optionally substituted by 1 or 2 hydroxy group(s),

p has a value of 0, 1 or 2,

R^2 stands for a nitro group, an amino group or a (C_{1-4} alkanoyl)amino group,

and pharmaceutically suitable acid addition salts thereof.

2. A 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative as claimed in Claim 1, wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a chloro atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a cyclopropyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two methyl group(s) or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom

as the heteroatom, and the heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 methoxy groups, or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 methoxy groups, n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group, and pharmaceutically suitable acid addition salts thereof.

3. A 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative as claimed in Claim 2, wherein

R^3 and R^4 represent, independently, a hydrogen atom, a cyclopropyl group, a methoxy group, an amino group, a dimethylaminophenyl group or a C_{1-2} alkyl group which latter is substituted by a phenyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl group, or

R^3 and R^4 form, together with the adjacent nitrogen atom and optionally a further nitrogen atom or oxygen atom, an imidazolyl, morpholino or piperazinyl group, wherein

the piperazinyl group is substituted by a methoxyphenyl group,
n has a value of 0 or 1,
m has a value of 0 or 1,
R^2 stands for a nitro group or an amino group,
A represents a hydrogen atom,
B means a hydrogen atom,
and pharmacêutically suitable acid addition salts thereof.

4. A 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative as claimed in Claim 3, wherein
R^3 represents a hydrogen atom,
R^4 stands for a cyclopropyl group, a methoxy group or an amino group,
n has a value of 0,
m has a value of 0,
R^2 means an amino group,
A represents a hydrogen atom,
B means a hydrogen atom,
and pharmaceutically suitable acid addition salts thereof.

5. A 8-methyl-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine derivative as claimed in Claim 1, wherein in formula I
A forms together with B a valence bond between the carbon atoms in positions 8 and 9,
R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein
R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a morpholino group, wherein the phenyl group is optionally substituted by one or two C_{1-2} alkoxy group(s), or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 2 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is optionally substituted by a halo atom or a C_{1-4} alkoxy group,

p has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group,

and pharmaceutically suitable acid addition salts thereof.

6. A 8-methyl-7H-1,3-dioxolo/4,5-h//2,3/-

benzodiazepine derivative as claimed in Claim 5, wherein

A forms together with B a valence bond between the carbon atoms in positions 8 and 9,

R^2 represents a nitro group or an amino group,

R^1 stands for a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 means a chloro atom, a phenoxy group, or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 represent, independently, a hydrogen atom, a guamyl group or a C_{1-3} alkyl group optionally substituted by a phenyl group, a dimethoxyphenyl group or a morpholino group, or

R^7 and R^8 form with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by one or two identical or different substituent(s) selected from the group consisting of a hydroxy group, a methoxyphenyl group, a fluorophenyl group, a benzyl group or a (methoxy-phenoxy)-(hydroxypropyl) group,

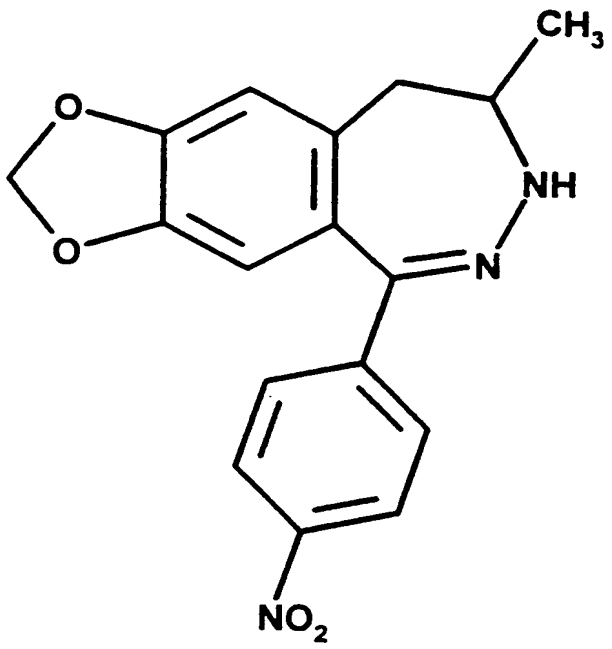
p has a value of 0, 1 or 2,

and pharmaceutically suitable acid addition salts thereof.

7. A 8-methyl-7H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine derivative as claimed in Claim 6, wherein
R^2 represents an amino group,
R^1, A and B are as defined in Claim 6,
and pharmaceutically suitable acid addition salts thereof.

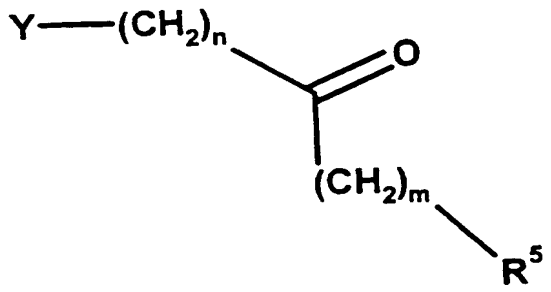
8. A process for the preparation of a 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein R^1 and R^2 are as defined in Claim 1, and pharmaceutically suitable acid addition salts thereof, characterized in that

a) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for a halo atom or a pyridyl group, n has a value of 0, 1 or 2, m has a value of 0, 1 or 2, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H--1,3-dioxolo/4,5-h//2,3/benzodiazepine of the formula III



III

is reacted with a reagent of the formula VI



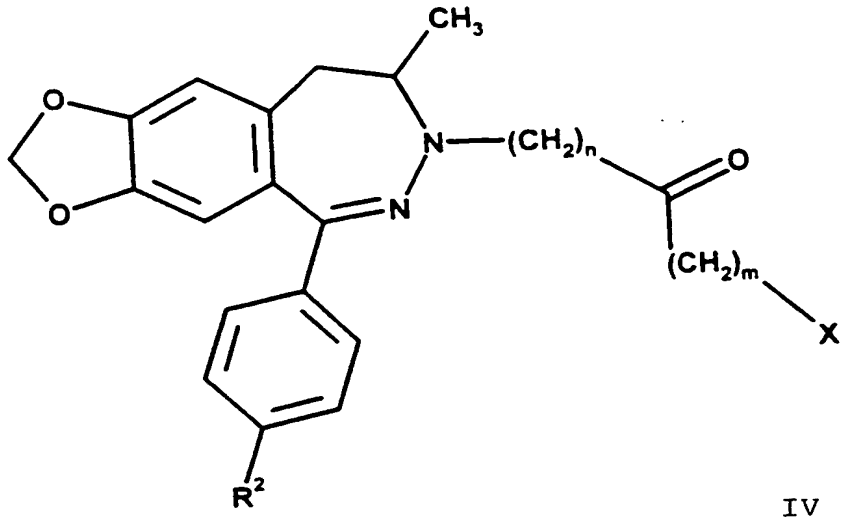
VI

wherein Y represents a leaving group, R^5 is a halo atom or a pyridyl group; or

b) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for an imidazolyl group, n has a value of 0, m has a value of 0, R^2 means a nitro group, A and B represent a

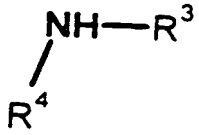
hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine of the formula III is reacted with 1,1'-carbonyldiimidazole; or

c) for the preparation of a compound of the formula I, wherein R^1 represents a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein R stands for a group of the formula $-NR^3R^4$, wherein R^3, R^4, n and m are as defined in connection with formula I, R^2 means a nitro group, A and B represent a hydrogen atom, the 7,8-dihydro-8-methyl-5-(4-nitrophenyl)--9H-1,3-dioxolo/4,5-h//2,3/benzodiazepine of the formula III is reacted with a reagent of the formula VI, wherein Y and R^5 represent, independently, a leaving group, n and m are as stated above, and the obtained benzodiazepine derivative of the formula IV



IV

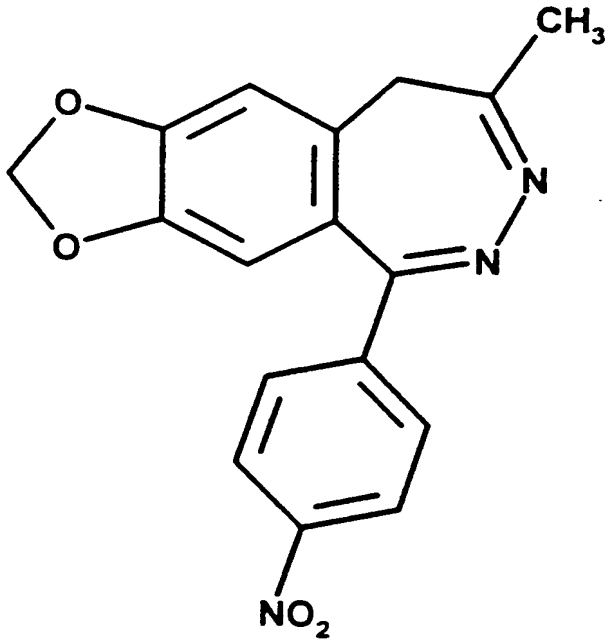
wherein X stands for a leaving group, n and m are as stated above, is reacted with an amine of the formula VII



VII

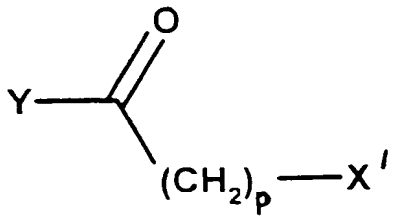
wherein R^3 and R^4 are as stated above; or

d) for the preparation of a compound of the formula I, wherein R^1 stands for a group of the formula $-CO-(CH_2)_p-R^6$, wherein R^6 represents a halo atom, a phenoxy group or a C_{1-4} alkoxy group, p has a value of 0, 1 or 2, A forms together with B a valence bond, R^2 means a nitro group, the 8-methyl--5-(4-nitrophenyl)-9H-1,3-dioxolo/4,5-h//2,3/-benzodiazepine of the formula II



II

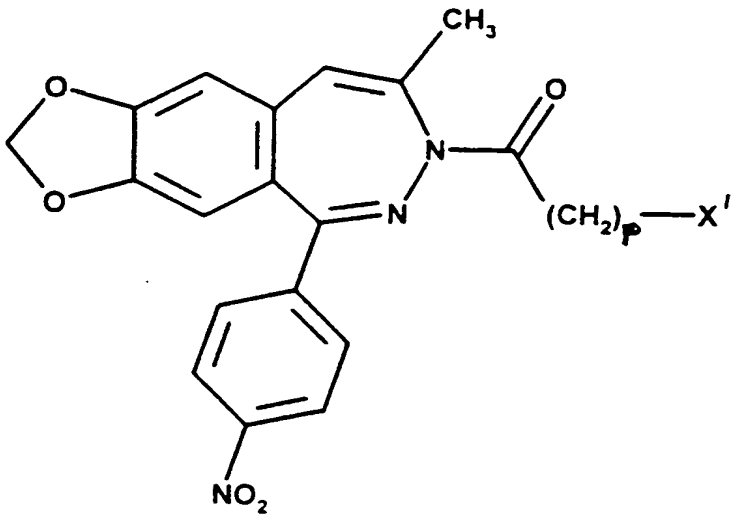
is reacted with an acylating agent of the formula IX



IX

wherein Y represents a leaving group, X' stands for a halo atom, a phenoxy group or a C_{1-4} alkoxy group, p has a value of 0, 1 or 2;
or

e) for the preparation of a compound of the formula I, wherein R^1 stands for a group of the formula $-CO-(CH_2)_p-R^6$, wherein R^6 represents a group of the formula $-NR^7R^8$, wherein R^7, R^8 and p are as defined in connection with the formula I, A forms together with B a valence bond, R^2 means a nitro group, the 8-methyl-5-(4-nitrophenyl)-9H-1,3-dioxolo-/4,5-h//2,3/benzodiazepine of the formula II is reacted with an acylating agent of the formula IX, wherein each of Y and X' represents, independently, a leaving group, p is as stated above, and the obtained acylated compound of the formula VIII



VIII

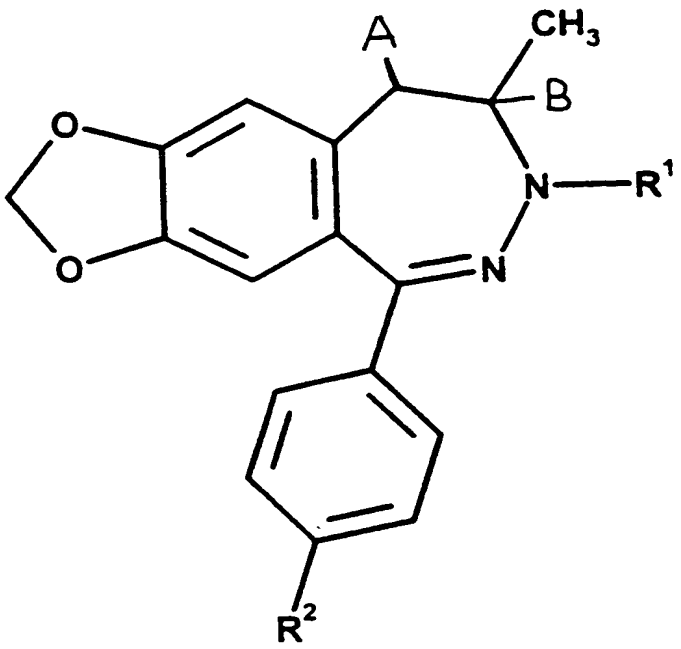
wherein X' and p are as defined above, is reacted with an amine of the formula HNR^7R^8, wherein R^7 and R^8 are as stated above;

and, if desired, an obtained compound of the formula I, wherein R^2 represents a nitro group, R^1, A and B are as defined in connection with the formula I, is transformed into a compound of the formula I, wherein R^2 stands for an amino group, by reduction;

and, if desired, an obtained compound of the formula I, wherein R^2 represents an amino group, R^1, A and B are as defined in connection with the formula I, is reacted with a C_{1-4} alkanecarboxylic acid or a reactive acylating derivative thereof;

and, if desired, an obtained base of the formula I is converted to a pharmaceutically suitable acid addition salt or liberated from the acid addition salt.

9. A pharmaceutical composition comprising a 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I



I

wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a C_{3-6} cycloalkyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two C_{1-4} alkyl group(s), a C_{1-4} alkyl group which latter is

optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 substituent(s), wherein the substituent consists of a C_{1-4} alkoxy group, or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 substituents, wherein the substituent is a C_{1-4} alkoxy group,

n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2, or

A forms together with B a valence bond between the carbon atoms in positions 8 and 9, and in this case

R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group, a C_{3-6} cycloalkyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C_{1-4} alkoxy group, or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 3 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is

optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a halo atom or a C_{1-4} alkoxy group, and, in case of the phenoxy(C_{1-4} alkyl) group, the alkyl group is optionally substituted by 1 or 2 hydroxy group(s),

p has a value of 0, 1 or 2,

R^2 stands for a nitro group, an amino group or a (C_{1-4} alkanoyl)amino group,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient and one or more conventional carrier(s).

10. A pharmaceutical composition as claimed in Claim 9 comprising a 1,3-dioxolo-/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a chloro atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a cyclopropyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two methyl group(s) or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated

heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and the heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 methoxy groups, or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 methoxy groups, n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group, or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

11. A pharmaceutical composition as claimed in Claim 10 comprising a 1,3-dioxolo-/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

R^3 and R^4 represent, independently, a hydrogen atom, a cyclopropyl group, a methoxy group, an amino group, a dimethylaminophenyl group or a C_{1-2} alkyl group which latter is substituted by a phenyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl

group, or

R^3 and R^4 form, together with the adjacent nitrogen atom and optionally a further nitrogen atom or oxygen atom, an imidazolyl, morpholino or piperazinyl group, wherein the piperazinyl group is substituted by a methoxyphenyl group,

n has a value of 0 or 1,

m has a value of 0 or 1,

R^2 stands for a nitro group or an amino group,

A represents a hydrogen atom,

B means a hydrogen atom,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

12. A pharmaceutical composition as claimed in Claim 11 comprising a 1,3-dioxolo-/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

R^3 represents a hydrogen atom,

R^4 stands for a cyclopropyl group, a methoxy group or an amino group,

n has a value of 0,

m has a value of 0,

R^2 means an amino group,

A represents a hydrogen atom,

B means a hydrogen atom,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

13. A pharmaceutical composition as claimed in Claim 9 comprising an 8-methyl--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

A forms together with B a valence bond between the carbon atoms in positions 8 and 9,

R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a morpholino group, wherein the phenyl group is optionally substituted by one or two C_{1-2} alkoxy group(s), or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 2 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed

the phenyl or phenoxy group is optionally substituted by a halo atom or a C_{1-4} alkoxy group,

p has a value of 0, 1 or 2,

R^2 stands for a nitro group or an amino group,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

14. A pharmaceutical composition as claimed in Claim 13 comprising an 8-methyl--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

A forms together with B a valence bond between the carbon atoms in positions 8 and 9,

R^2 represents a nitro group or an amino group,

R^1 stands for a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 means a chloro atom, a phenoxy group, or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 represent, independently, a hydrogen atom, a guamyl group or a C_{1-3} alkyl group optionally substituted by a phenyl group, a dimethoxyphenyl group or a morpholino group, or

R^7 and R^8 form with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group or a saturated heterocyclic group having 5 or 6 members and comprising one or two nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom,

and said heterocyclic group is optionally substituted by one or two identical or different substituent(s) selected from the group consisting of a hydroxy group, a methoxyphenyl group, a fluorophenyl group, a benzyl group or a (methoxyphenoxy)-(hydroxypropyl) group,

p has a value of 0, 1 or 2,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

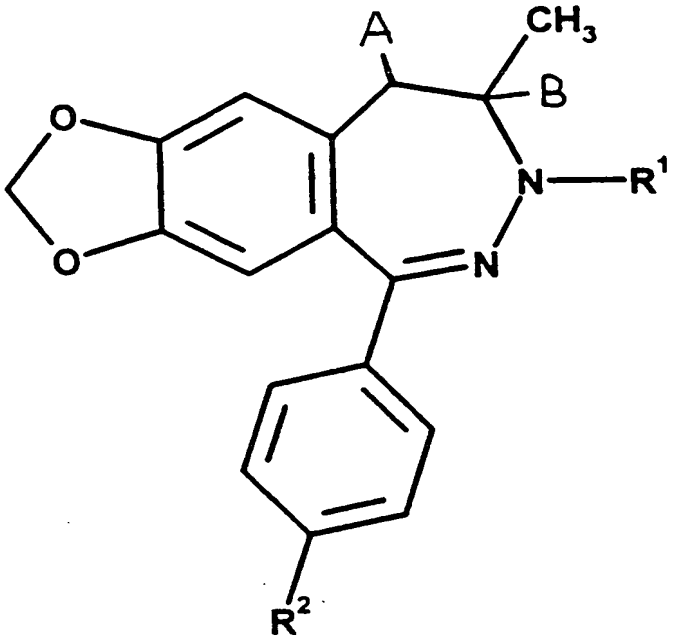
15. A pharmaceutical composition as claimed in Claim 14 comprising an 8-methyl--7H-1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I, wherein

R^2 represents an amino group,

R^1, A and B are as defined in Claim 6,

or a pharmaceutically suitable acid addition salt thereof as the active ingredient.

16. A method of treatment in which a patient suffering especially from epilepsy or a neurodegenerative disease or being in a state after stroke is treated with a non-toxic dose of a 1,3-dioxolo/4,5-h//2,3/benzodiazepine derivative of the formula I



I

wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a C_{3-6} cycloalkyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two C_{1-4} alkyl group(s), a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and

comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 substituent(s), wherein the substituent consists of a C_{1-4} alkoxy group, or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that is optionally substituted by 1 to 3 substituents, wherein the substituent is a C_{1-4} alkoxy group,

n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2, or

A forms together with B a valence bond between the carbon atoms in positions 8 and 9, and in this case

R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group, a C_{3-6} cycloalkyl group or a C_{1-4} alkyl group

which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C_{1-4} alkoxy group, or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 3 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a halo

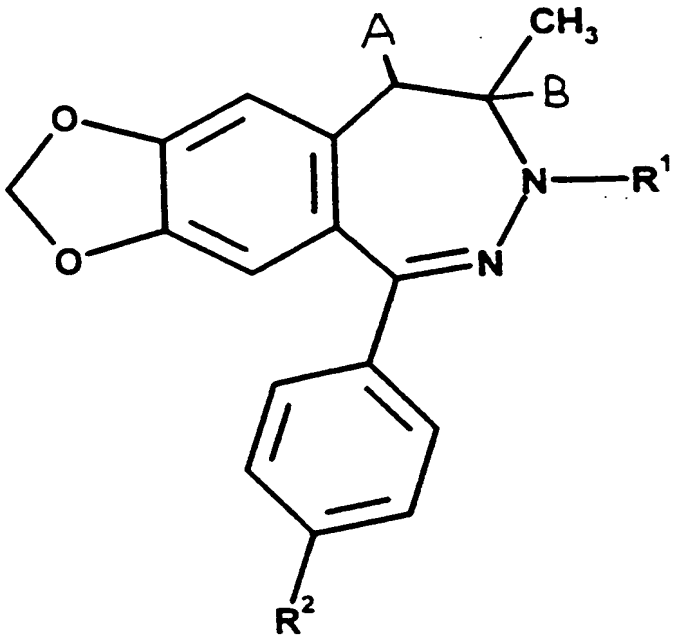
atom or a C_{1-4} alkoxy group, and, in case of the phenoxy(C_{1-4} alkyl) group, the alkyl group is optionally substituted by 1 or 2 hydroxy group(s),

p has a value of 0, 1 or 2,

R^2 stands for a nitro group, an amino group or a (C_{1-4} alkanoyl)amino group,

or a pharmaceutically suitable acid addition salt thereof.

17. A process for preparing a pharmaceutical composition suitable for the treatment of especially epilepsy, a neuro-degenerative disease or a state after stroke, characterized in that a 1,3-dioxolo/4,5-h/-/2,3/benzodiazepine derivative of the formula I



I

wherein

A represents a hydrogen atom,

B means a hydrogen atom,

R^1 stands for a group of the formula $-(CH_2)_n-CO-(CH_2)_m-R$, wherein

R represents a halo atom, a pyridyl group or a group of the formula $-NR^3R^4$, wherein

R^3 and R^4 mean, independently, a hydrogen atom, a C_{3-6} cycloalkyl group, a C_{1-4} alkoxy group, an amino group, a phenyl group optionally substituted by one or two C_{1-4} alkyl group(s), a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising 1 to 3 nitrogen atom(s) or a nitrogen atom and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by a phenyl group which latter is optionally substituted by 1 to 3 substituent(s), wherein the substituent consists of a C_{1-4} alkoxy group, or

R^3 and R^4 form, with the adjacent nitrogen atom and optionally with a further nitrogen atom or an oxygen atom, a saturated or unsaturated heterocyclic group having 5 or 6 members, being optionally substituted by a phenyl group that

is optionally substituted by 1 to 3 substituents, wherein the substituent is a C_{1-4} alkoxy group,

n has a value of 0, 1 or 2,

m has a value of 0, 1 or 2, or

A forms together with B a valence bond between the carbon atoms in positions 8 and 9, and in this case

R^1 represents a group of the formula $-CO-(CH_2)_p-R^6$, wherein

R^6 stands for a halo atom, a phenoxy group, a C_{1-4} alkoxy group or a group of the formula $-NR^7R^8$, wherein

R^7 and R^8 mean, independently, a hydrogen atom, a guanyl group, a C_{3-6} cycloalkyl group or a C_{1-4} alkyl group which latter is optionally substituted by a phenyl group or a saturated heterocyclic group having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, wherein the phenyl group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a C_{1-4} alkoxy group, or

R^7 and R^8 form together with the adjacent nitrogen atom an oxopyrrolidinyl group, a phthalimido group which latter is optionally substituted, or a saturated heterocyclic group

having 5 or 6 members and comprising one or more nitrogen atom(s) or a nitrogen and an oxygen atom as the heteroatom, and said heterocyclic group is optionally substituted by 1 to 3 identical or different substituent(s) selected from the group consisting of a hydroxy group, a phenyl group, a phenoxy group, a phenyl(C_{1-4} alkyl) group or a phenoxy(C_{1-4} alkyl) group, wherein in case of the substituents listed the phenyl or phenoxy group is optionally substituted by 1 to 3 identical or different substituent(s), wherein the substituent is a halo atom or a C_{1-4} alkoxy group, and, in case of the phenoxy(C_{1-4} alkyl) group, the alkyl group is optionally substituted by 1 or 2 hydroxy group(s),

p has a value of 0, 1 or 2,

R^2 stands for a nitro group, an amino group or a (C_{1-4} alkanoyl)amino group,

or a pharmaceutically suitable acid addition salt thereof, together with one or more conventional carrier(s), is converted to a pharmaceutical composition.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/HU 98/00076

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/04 A61K31/55

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 699 678 A (LILLY CO ELI) 6 March 1996 see claim 1	1-14
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
26 October 1998	19/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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